

From the Department of Vascular Surgery
Center of Molecular Medicine and Surgery
Karolinska Institutet

BLEEDING IN ABDOMINAL AORTIC ANEURYSM REPAIR

Carl Montán



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The cover picture *Dashboard for surgery* illustrates a synthesis of the conclusions in this thesis. Design by the author and Veronika Csorba.

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Bleeding in Abdominal Aortic Aneurysm Repair

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Carl Montán, MD

Principal Supervisor:

Associate Professor Carl Magnus Wahlgren, MD
Karolinska Institutet
Department of Molecular Medicine and Surgery
Department of Vascular Surgery

Co-supervisors:

Associate Professor Jan Holst, MD
Lund University
Department of Clinical Sciences
Department of Vascular Surgery

Professor Ulf Hedin, MD
Karolinska Institutet
Department of Molecular Medicine and Surgery
Department of Vascular Surgery

Opponent:

Professor Anders Jeppsson, M.D
University of Gothenburg, Sahlgrenska Academy
Department of Molecular and Clinical Medicine
Department of Thoracic Surgery

Examination Board:

Professor Christer Svensén, MD
Karolinska Institutet
Department of Clinical Science and Education
Södersjukhuset, Karolinska Institutet

Professor Torbjörn Ivert, MD
Karolinska Institutet
Department of Molecular Medicine and Surgery
Department of Thoracic Surgery

Associate Professor Mårten Falkenberg, MD
University of Gothenburg, Sahlgrenska Academy
Institute of Clinical Sciences
Department of Radiology

To My Family

“For myself, I am an optimist – it does not seem to be much use being anything else.”

Winston Churchill

PREFACE

“Why study bleeding in abdominal aortic aneurysm repair? Is the problem not already solved? We already know that bleeding in general is bad and leads to a worse outcome, and it is of course obvious that massive bleeding is life threatening!”

“Do we really need to evaluate how we treat bleeding? Just transfuse the patient and stop the bleeding!”

“In the era of endovascular repair bleeding in abdominal aortic aneurysm repair is no longer an issue!”

-During this thesis project I have come across these questions and statements from colleagues and myself. Given the future lives that are at stake in the treatment of abdominal aortic aneurysms, the above questions demand firm answers. Hence the following...

ABSTRACT

Background and aims:

Massive bleeding in open abdominal aortic aneurysm (AAA) repair is associated with worse outcome. However, few studies have investigated specific problems related to perioperative bleeding and blood transfusion in elective or emergent AAA repair with open (OR) or endovascular (EVAR) aneurysm repair. The overall aim of this thesis project was to investigate the clinical problem of bleeding in open and endovascular repair in both ruptured and elective AAA, including treatment of bleeding and association to risk factors and outcome in this patient group.

Patients and Methods:

The studies were retrospective and based on medical records (all) and regional and national registries (Papers II-IV). **Paper I** studied the Fascia Suture Technique (FST) as closure method for hemostasis in 160 femoral access sites after EVAR in AAA patients. **Paper II** investigated ruptured (rAAA) and non-rAAA cases undergoing EVAR in 525 patients. Perioperative bleeding and the association to mortality and morbidity was investigated. **Paper III** investigated preoperative coagulation tests and their association to preoperative hypotension and perioperative bleeding and outcome in 91 rAAA patients. **Paper IV** studied blood transfusion in 369 ruptured AAA (rAAA) patients undergoing OR or EVAR. Timing of blood transfusion and time dependent ratios of blood products were studied and related to method of repair and outcome.

Results:

In **Paper I** FST was associated with a 91% success rate. Complications were two pseudoaneurysms (PA) at 30-day follow-up and nine <1cm PA at 1-year. No specific preoperative risk factor for failure of the method was found. In **Paper II** a perioperative bleeding of >2 liters was independently associated with increased mortality (non-rAAA patients odds ratio 30; 95% CI [3.6, 145], rAAA patients odds ratio 10.7; 95% CI [3.2, 36.1]) and morbidity in non- and rAAA cases. Open femoral access, branched EVAR and larger diameter introducers were associated with increased perioperative blood loss. In **Paper III** low preoperative fibrinogen concentration (<1.5 g/L) was significantly associated with preoperative hypotension (systolic blood pressure <70 mmHg), increased perioperative bleeding and worse outcome after rAAA. In **Paper IV** delayed platelet transfusion (>1h) was associated with increased mortality in rAAA patients requiring massive transfusion (>10 units within 24 h or 4 units within 1 h). Fifty-five percent of rAAA patients repaired by EVAR received massive transfusion. Transfusion ratios of 1:1 for fresh frozen plasma (FFP):red blood cells (RBC) were associated with lower mortality. Ratios of platelets (PLT):RBC increased significantly over the study period.

Conclusions:

- Fascia Suture Technique proved feasible and safe with a low complication rate. Introducer size had no impact on outcome. No preoperative risk factors for failure were found.
- A perioperative blood loss exceeding 2 liters in EVAR was independently associated with increased mortality and morbidity in both acute and elective AAA patients. Procedural risk factors for increased perioperative bleeding were open femoral access, fascia suture technique, branched stent grafts and aneurysm diameter.
- Preoperative fibrinogen concentrations below 1.5 g/L were associated with a ten-fold increased risk of perioperative bleeding of more than 2 liters in rAAA. Low fibrinogen concentration should be suspected in patients with preoperative hypotension.
- A ratio FFP: RBC close to 1:1 in EVAR and open repaired patients was associated with lower mortality.
- Delayed (>1h) platelet transfusion was associated with significantly increased mortality. Ratios of PLT:RBC have increased over the last years.
- Transfusion strategies in patients undergoing rAAA treatment with EVAR or open repair need further research. Also the definitive role of fibrinogen in patients with rAAA and hemodynamic shock need to be investigated in future studies.

Keywords: Bleeding, Abdominal Aortic Aneurysm, Massive Transfusion, Hemostasis, Fascia Suture Technique, Endovascular Aortic Aneurysm Repair, Open Repair

® Carl Montán, 2015

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following scientific papers, which will be referred to in the text by their Roman numerals:

- I. **Short- and Midterm Results of the Fascia Suture Technique for Closure of Femoral Artery Access Sites After Endovascular Aneurysm Repair**
Carl Montán, Leena Lehti, Jan Holst, Katarina Björse and Timothy A. Resch
Journal of Endovascular Therapy, December 2011, Volume 18, Number 6, Pages 789-796
- II. **Perioperative Hemorrhage in Endovascular Abdominal Aneurysm Repair Affects Outcome**
Carl Montán, Marcus Wannberg, Jan Holst and Carl Magnus Wahlgren
European Journal of Vascular and Endovascular Surgery, July 2013, Volume 46, Issue 1, Pages 87–92
- III. **Preoperative hypofibrinogenemia is associated with increased intraoperative bleeding in ruptured abdominal aortic aneurysms**
Carl Montán, Fredrik Johansson, Ulf Hedin and Carl Magnus Wahlgren
Thrombosis Research, March 2015, Volume 135, Issue 3, Pages 443-448
- IV. **Massive blood transfusion in patients with ruptured abdominal aortic aneurysms**
Carl Montán, Ulf Hammar, Agneta Wikman, Eva Berlin, Jan Holst, Jonas Malmstedt and Carl Magnus Wahlgren
Manuscript Submitted

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LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
ACS	Abdominal Compartment Syndrome
ACT	Activated Clotting Time
ADP	Adenosine Diphosphate
APTT	Activated Partial Thromboplastin Time
BP	Blood Pressure
Ca ²⁺	Calcium ions
CFT	Clot Formation Time
CI	Confidence Interval
COX	Cyclo-oxygenase
CT	Computed Tomography
CT	Clotting Time
CTA	Computed Tomography Angiography
DM	Diabetes Mellitus
ECM	Extracellular Matrix
EVAR	Endovascular Aortic Aneurysm Repair
F +roman number	(Coagulation) Factor and its number
F +roman number +a	Activated Factor and its number
FFP	Fresh Frozen Plasma
FFP:RBC	Ratio of units of Fresh Frozen Plasma to Red Blood Cells
FII	Prothrombin (Factor II)
Fr	French (diameter size of catheters and introducers)
g/L	Gram per Liter
GPIIb/IIIa	Glycoprotein IIb/IIIa
h	Hours
Hb	Hemoglobin
HR	Heart Rate
Il	Interleukin
IOB	Intraoperative/Perioperative Bleeding

IQR	Inter Quartile Range
IU	International Units
LMWH	Low Molecular Weight Heparin
LRT	Little Red Tube
MI	Myocardial Infarction
ml	Milliliter
mmol/L	Millimoles per Liter
MOF	Multi Organ Failure
MRI	Magnetic Resonance Imaging
MT	Massive Transfusion
NSAID	Non-Steroid Anti-Inflammatory Drug
OR	Open Repair
OR	Odds Ratio
P2Y ₁₂	G-protein and receptor found mainly on platelets
PFA	Platelet Function Analysis
PLT	Platelets
PLT:RBC	Ratio of units of Platelets to Red Blood Cells
PTr-INR	Prothrombin Time ratio-International Normalized Ratio
rAAA	Ruptured Abdominal Aortic Aneurysm
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
rFVIIa	Recombinant Factor VIIa
ROTEM	Rotational Thromboelastometry
s	Seconds
SD	Standard Deviation
TEG	Thromboelastography
TF	Tissue Factor
TFPI	Tissue Factor Pathway Inhibitor
TXA ₂	Thromboxane A ₂
u	Unit(s)

1 INTRODUCTION

1.1 BACKGROUND

Abdominal Aortic Aneurysm (AAA) is common in the aging population and ruptured AAA is a major cause of death. In open aortic surgery, massive blood loss is associated with increased mortality.^{1,2} In elective cases, AAA repair by open and endovascular methods are relatively safe procedures, but nevertheless associated with a high risk of perioperative bleeding. In emergencies from ruptured abdominal aortic aneurysm, massive bleeding is one of the toughest challenges a surgeon and his or her team can encounter where blood loss can be considerable before control is achieved.

Bleeding in AAA repair has impact on both mortality and morbidity. Although extensive knowledge has been gained in the fields of hemostasis, coagulopathy and treatment of massive bleeding, few studies have focused on bleeding in AAA repair. Little is known about bleeding complications in the era of endovascular repair and risk factors for such complications are largely unknown. Transfusion strategies to manage bleeding in emergencies have evolved during the recent decades but few investigations have assessed the applicability to bleeding AAA patients.

EVAR is an established method of treatment of infrarenal AAA.³ Blood loss in elective EVAR is most commonly a result of leakage from guide wire and sheath exchanges, and from complications during access site closure. The femoral access sites are the main concern for bleeding and previous studies have investigated perioperative bleeding related to closure devices and other methods of access site closure.⁴⁻⁷

The purpose of this thesis has been to investigate key components of bleeding in AAA repair. The four scientific papers investigate practical issues, risk factors, and predictors of bleeding as well as the treatment of bleeding associated with both non-ruptured and ruptured AAA in open and endovascular repair.

1.2 HISTORICAL NOTES

Arterial aneurysms were first described in the Eber Scrolls from Egypt in 1550 BC and in Sushruta from India 800-60 BC.^{8,9} Methods of treatment of Abdominal Aortic Aneurysms have included attempts to ligate the aorta first practiced by the Greek surgeon Antyllus 126-216 AD.¹⁰ The method remained the preferred option up until the nineteenth century.¹¹⁻¹³ Inducing thrombosis of the aneurysm by wires was attempted by Moore and Murchison in 1864.¹³ In 1948 Nissen and colleges wrapped the AAA of Albert Einstein with cellophane to induce a fibrotic process and hinder further expansion of the aneurysm.¹⁴ In 1951 Dubost performed the first AAA resection with restoration of arterial blood flow.¹⁵ Freeman reported the first successful resection and bypass of an AAA, using autologous vein in 1951.¹⁶ Voorhees and Blakemore and Shumacker were first to describe the use of artificial grafts for AAA treatment in humans.^{17,18}

In 1986 a new method of endovascular repair was described by the Ukrainian surgeon Volodos, however it was not until the Argentinian surgeon Parodi described it in English in 1991 that the method gained worldwide fame.^{19,20}

It is believed that Plato (≈428-348 BC) first described the ability of blood to form fibers when outside the blood vessel.²¹ In 1865 platelets and their critical function in hemostasis were discovered.^{22,23} By the 1960' many components in coagulation had been described and also the concept of the coagulation *cascade* or *waterfall* of events.^{24,25} In the last decades further knowledge has been gained in the very complex mechanisms of hemostasis.²⁶

The first blood transfusions are attributed to physicians Colle from Italy in 1628 and the Frenchman Denis in 1666.^{27,28} At the same time in England, Lower was one of the pioneers in the field of transfusion.²⁹ Obstetrician Blundell understood that an incompatibility of human blood transfusion to some patients existed but could not explain why. Dr. Blundell performed successful human to human transfusions in 1825.³⁰ However, it was not until Karl Landsteiner discovered the blood groups in 1900 and the Rh factor in 1940 that blood transfusions became safer.³¹ Blood transfusion has historically been controversial as it implies giving and accepting living cells from one or more donors. In some cultures and religions blood transfusions remain controversial.³²

1.3 ABDOMINAL AORTIC ANEURYSMS

1.3.1 Definition and pathogenesis

An aneurysm is most commonly defined as a localized widening of all the layers (intima, media and adventitia) of the artery wall exceeding at least 50 % of the normal expected diameter.³³ True aneurysms differ from vascular ectasies that are described as a continuous non-localized enlargement of the diameter of the vessel. Pseudo-aneurysms, also referred to as false aneurysms, are defined as a circumscribed hematoma formed outside the arterial wall due to a defect in the artery, often formed after penetrating or blunt injury to the vessel. Dramatic deceleration forces can lead to substantial aortic injuries and rupture, often with deadly outcome.³⁴

Aneurysms can expand in a fusiform (includes the expansion of the whole circumference) or saccular (expansion of a partial circumference of the vascular wall) way.^{35,36} The etiology of saccular aneurysms have been suggested to be different to that of fusiform aneurysms often related to mycotic aneurysms (due to inflammatory or infectious events) or trauma.³⁷

Abdominal aortic aneurysms are defined as aneurysms below the anatomic landmark of the diaphragm. Aneurysms that include the aorta above the diaphragm are referred to as thoracic or thoracoabdominal if they include both the thoracic and abdominal parts. Thoracic aortic aneurysms are different from abdominal aortic aneurysms; possibly explained by biomechanical factors, differences in the origin of the smooth muscle cells and differences in the structure of the aortic wall (capillaries/vasa vasorum penetrate into the media in thoracic but not abdominal aorta). Abdominal aortic aneurysms can be described as infrarenal, juxtarenal or suprarenal. Suprarenal abdominal aneurysms could also be included in thoracoabdominal aortic aneurysms.³⁸

An abdominal aortic aneurysm is most commonly defined as a diameter expansion of the abdominal aorta exceeding 30 mm.³⁹ The fundamentals for this definition are based on the works by Steinberg and Stein in 1966 and Leopold in 1970.^{40,41} The definition is used in the UKSAT and ADAM trials.^{42,43} Sterpetti in 1987 defined infrarenal AAA as having a ratio of >1.5 calculated by the diameter of the infrarenal aorta divided by the diameter of the suprarenal aorta.⁴⁴ Alternatively AAA can be defined as a 50 % dilatation of the expected normal artery diameter as described by Johnston et al. 1991, a definition used by the International Society for Cardiovascular Surgery.⁴⁵ The ambiguous definitions of AAA have contributed to differences in epidemiology reports and clinical practice.⁴⁶

Aneurysms develop through a series of histopathological changes that lead to a weakening of the vascular wall. Inflammatory processes are thought to be key contributors to the histopathological changes.⁴⁷⁻⁴⁹ Inflammatory cells release proteolytic enzymes, which degrade elastin and collagen and promote apoptosis of smooth muscle cells in the media. This process affects the structural integrity of the vessel wall.^{50,51,52} In addition, the formation of a

mural thrombus in the dilated vessel segment has been shown to enhance structural deterioration of the underlying aortic wall, which promote aneurysm growth and risk of rupture.⁵³

*Definitions below according to Rutherford.*³³

1.3.1.1 Non-ruptured asymptomatic abdominal aortic aneurysm

Non-ruptured asymptomatic AAAs are intact AAAs in patients without symptoms of pain or rupture by clinical examination and/or diagnostic imaging.

1.3.1.2 Symptomatic abdominal aortic aneurysm

Non-ruptured symptomatic AAAs are intact AAAs in patients with symptoms of abdominal, back or chest pain by medical history or clinical examination with tenderness over the aneurysm upon palpation.

1.3.1.3 Ruptured abdominal aortic aneurysm

Ruptured AAAs (rAAA) presents with signs of a rupture in the vascular wall leading to a hematoma outside the vascular wall. The rupture can be contained in the retroperitoneal space or be non-contained with massive intraperitoneal bleeding. The most common site of rupture is to the posterior left of the AAA.³³ Ruptured AAA usually cause severe pain in the abdomen, back or chest.

1.3.2 Epidemiology

The epidemiology of AAA has been studied thoroughly through population based screening and necropsy studies.⁵⁴⁻⁵⁷ The prevalence of AAA among men 64-83 years was found to be 4.0-7.6% in large randomized screening studies in the UK (Chichester 1995 and MASS 2002), in Denmark 1998 and in Australia 2000 (extra data presented 2004).^{41,42,58,59,60} Recent Swedish reports from screening programs have suggested lower prevalence rates of 0.4%-1.7%.⁶¹⁻⁶³

In women the prevalence of AAA is lower than for males. According to a Swedish study in 2013 the prevalence was only 0.5% among 70 year old women.⁶³ There are indications that women with AAA are more susceptible to rupture and have associated higher 30-day mortality rate after repair compared to males.⁶⁴⁻⁶⁶

Independent risk factors for developing an AAA have been suggested by numerous authors.⁶⁷⁻⁷⁵ The most commonly described risk factors are; age, gender, height, family history of AAA, smoking, hypertension, coronary artery disease, hyperlipidemia, chronic and obstructive pulmonary disease. It should be noted that most studies are performed on white male Caucasians and that other ethnic groups have a different prevalence of AAA.^{67,76}

Symptomatic AAAs are reported to constitute 5.5%-22% of all AAAs that require repair.⁷⁷⁻⁷⁹

The incidence of rAAA varies in studies and increases significantly with age.⁸⁰ In 1999 Chosky et al. reported an incidence of 76 per 100,000 for men over 50 years and 11 per 100,000 for women over 50 years.⁸¹ A report from Sweden 2006 describes incidences of AAA to be 10.6 per 100,000 over-all, 46 per 100,000 for males aged 60-69 and for males 70-79 years the incidence was 117 per 100,000 patient years.⁸⁰

A thorough medical history and physical examination should be performed in order to assess risk prediction for repair of AAA. Multiple risk prediction models have been developed and proven to be useful in assessing risk for mortality and morbidity.⁸² Patients that are deemed with a high procedural risk might be suggested to abstain from repair. It has been suggested to develop different risk prediction models for OR and EVAR.⁸²

1.3.3 Diagnosis and imaging

It is difficult to diagnose an asymptomatic AAA solely by clinical examination and medical history. An AAA can exist for many years without causing any clinical symptoms. Some patients experience a pulsation in the abdomen and AAAs can be diagnosed through palpation of a pulsating mass in the upper abdomen. It is however not a reliable method for diagnosis.⁸³ Studies have shown ultrasound (US) to be a better method than palpation to diagnose AAA.^{83,84} Symptomatic and ruptured AAA usually gives symptoms as described above.³³ AAA imaging through US, computed tomography (CT) or magnetic resonance imaging (MRI) has been compared.⁸⁵ Ultrasound is not as sensitive as CT and MRI for AAA diagnosis especially in obese patients with proximal aneurysms. In *Figure 1* three different techniques for the diagnosis of AAA are illustrated.

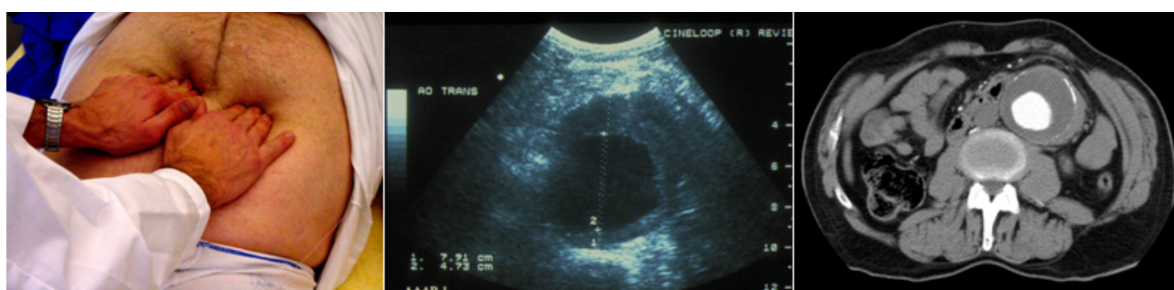


Figure 1. Diagnosis of Abdominal Aortic Aneurysm by, palpation, ultrasound and computer tomography. Pictures used with the courtesy of the copyright holder.

CT is the gold standard for measuring the diameter of AAA. The outer abdominal aortic wall is measured in cm and mm. CT is a very exact method in which the images are stored and can be used for planning in an eventual repair. However, CT is costly and overuse is potentially harmful as it might cause cancer.⁸⁶ MRI is also an accurate method for measuring the aorta, but the method is not as accessible as CT and takes longer time to perform. MRI protocols for evaluating the morphology of the AAA and the intraluminal thrombus are being developed and evaluated.^{87,88} These methods might prove to be important for rupture prediction and better understanding of pathogenesis.

The diameter of AAAs can also be measured by US. The main advantages of US are accessibility, and the use of non-harmful ultrasound waves. The disadvantages are

measurement variance between US users and that the diameter estimation is not as exact as CT.⁸⁹ Three different ways of measuring diameter with US have been described and debated. See *Figure 2*.

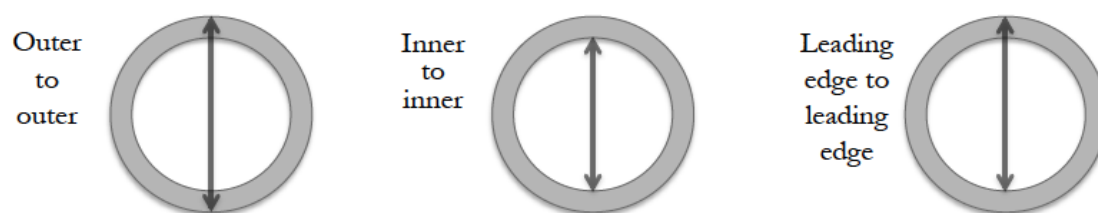


Figure 2. Techniques for measuring the diameter of the aorta by ultrasound

The *outer to outer* diameter is said to resemble the measurements of CT most correctly and has gained wide international use.⁴² However, some argue that the posterior outer diameter often is difficult to visualize properly. *Inner to inner* diameter is a measurement that has been criticized by some as inaccurate, as too small diameters are measured especially if an intraluminal thrombus is mistakenly perceived as the inner wall. One comparative study and a review could not detect significant differences in inter-observer variability between different US measuring methods.^{90,91} *Leading edge to leading edge* is the method used in Swedish AAA screening programs.^{92,93}

In AAA surveillance programs, US has clear advantages over CT because of its accessibility. US has also been suggested as a valid method for postoperative follow-up to measure postoperative AAA diameter after EVAR after the first year CT control.⁹⁴

1.3.4 Indications for treatment

1.3.4.1 AAA

The indications for repair of AAAs have been debated over many years and an international variation still exists. According to large trials repair of AAAs is recommended for men at diameters above 5.5 cm and in women at 5 cm and above.^{95,96} Age and comorbidities such as cardiac and pulmonary disease, hypertension, previous stroke, tumor disease, and other chronic diseases are factors that influence life expectancy and needs consideration before deciding upon repair and repair method.^{82,97}

1.3.4.2 Symptomatic AAA

Indications for repair of symptomatic AAAs are not based on diameter but on the symptoms, sometimes together with radiological findings. Abdominal and/or back pain together with a tenderness of the aneurysm upon palpation constitutes the symptoms.⁷⁹

1.3.4.3 Ruptured AAA

In health care systems, the treatment of rAAAs strains the organization to the maximum.⁹⁸ The time from rupture to treatment is one of the keys to success. Therefore, the primary

action should always be to care for the patient as if repair was to be performed as quickly as possible. Untreated rAAAs almost always leads to the death of the patient. However, the indication to repair a rAAA also requires an active decision that the procedure is beneficial to the patient.⁹⁷ In general, treatment is not controversial, but some elderly patients or patients with serious comorbidities with known AAA or unknown AAA may reject treatment in case of a life threatening event and decisions should be anchored with the patient and close relatives if possible. There are patients who survive a rupture without surgical treatment for many years.

1.3.5 Treatment of AAA

1.3.5.1 Open repair

Open repair is most commonly carried out through a midline abdominal incision and a transperitoneal approach. The retroperitoneum is incised and the structures overlaying the aorta are carefully dissected. After proximal and distal control of the aorta and its branches where the vascular wall is free from aneurysm, the aorta is opened in a longitudinal fashion. Back bleeding lumbar arteries and the inferior mesenteric artery (IMA) are over sewn (if indicated). A synthetic straight or bifurcated graft of appropriate size is then is sewn into the aorta and its branches as appropriate by continuous sutures of 3-0 Prolene or similar suture material. See *Figure 3*. The surgery is performed under general anesthesia. The operating time varies greatly depending on the anatomical position of the aneurysm and other factors. A retroperitoneal approach by a left subcostal transverse incision is often suggested for open surgery of AAA where a supra renal or supra coeliac clamping is required. It has by some authors been shown to be associated with less perioperative bleeding.⁹⁹

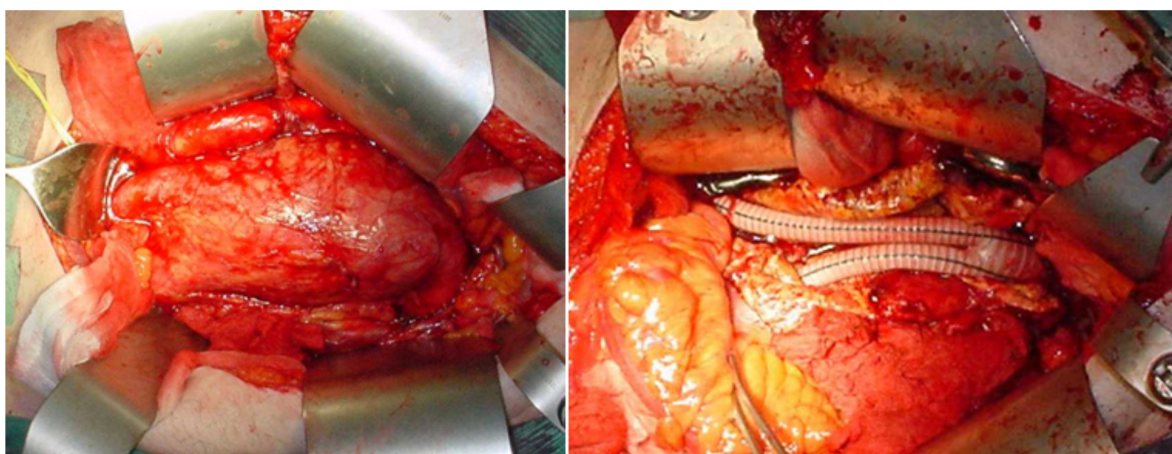


Figure 3. Open surgery of an abdominal aortic aneurysm, in the picture to the right a bifurcated graft has been sewn into the aorta. Pictures used with the courtesy of the copyright holder.

1.3.5.2 Endovascular repair

EVAR can be performed under general or local anesthesia.¹⁰⁰ The endovascular graft can be bifurcated or a uni-iliac. A bifurcated reconstruction is normally the preferred choice. In the setting of preoperative unilateral iliac obstruction, a uni-iliac stent graft is an option. In the

case of acute rupture without adequate possible sizing of a bifurcated graft a uni-iliac stent graft can be used. A femoral-femoral bypass should then also be performed to maintain blood flow to the contralateral leg. There are now many different manufacturers of stentgrafts approved for the reconstruction of AAA and care should be taken in selecting the most suitable for the individual patient.^{101,102}

Before the procedure, a careful planning is required in selecting the appropriate stent graft for the anatomy, status and physiology of the patient. CT angiography (CTA), with thin (<1 mm) slices and image reconstruction in several planes, is the preferred diagnostic method to plan the procedure and make necessary measurements.¹⁰¹ See *Figure 4*.

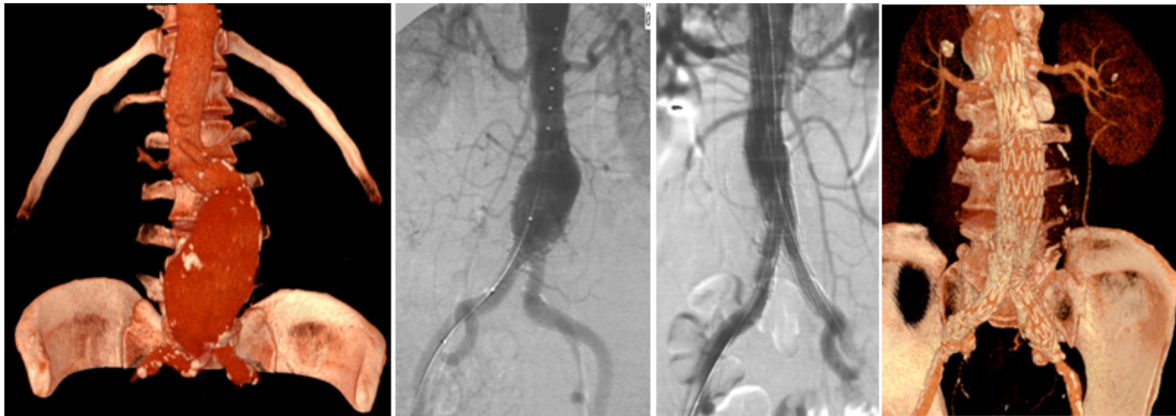


Figure 4. (Left to right) Computer tomography angiography (CTA) with 3D reconstruction of an abdominal aortic aneurysm, aortic angiogram under the endovascular aortic aneurysm repair procedure followed by CTA 3D reconstruction of stent graft in place. Pictures used with the courtesy of copyright holder.

The synthetic aortic stentgraft is delivered into the aorta and iliac arteries by pre-packed introducer devices of various sorts. The main body is usually delivered through one of the femoral arteries that is chosen to be the ipsilateral side.

Access to the common femoral arteries can be performed by percutaneous puncture using the Seldinger technique.¹⁰³ The percutaneous puncture is preferably made under guidance of ultrasound or X-ray.^{104,105,106} The aim should be to enter the femoral artery in the mid section between the epigastric artery and the bifurcation. A puncture on the most frontal part of the artery's circumference should be attempted.^{104,106} Access to the femoral arteries can also be performed through open surgical exposure.

Via the contralateral femoral artery, the distal stent graft of the contralateral side is delivered. The recommended measurements for the proximal and distal sealing zones as well as for the overlap between contralateral stent graft and elongation stent grafts on the ipsilateral side differ between stent grafts.¹⁰² A completion angiography is performed to ensure the correct placement of the device, without stenosis or kinking and proximal and distal sealing without endoleakage. Special care is taken to visualize the coeliac trunk, renal-, superior mesenteric-, and internal iliac arteries to make sure that they are patent.

After the procedure, closure of the femoral and/or other access sites is performed using open surgical exposure (cut down), suture mediated closure devices or fascia suture technique.

The closure device most commonly used and described in literature is the ProStarXL[®] (for large diameter access double devices are used). This technique is performed by deploying sutures in the vascular wall at the puncture site via a special device in the beginning of the EVAR procedure. In the end of the procedure the sutures are tied together to obtain hemostasis. The technique is referred to as the preclose technique.^{107,108}

In case of postoperative minor bleeding a device called FemoStop[®] can be applied for hemostasis.^{106,109} The FemoStop[®] holds pressure on top of the femoral access site in order for the puncture hole to seal. Postoperatively the distal pulses should be controlled in order to assure that no iatrogenic injury or thrombosis has occurred.

1.3.6 Outcome AAA treatment

Due to the severity and complexity of the diagnosis of AAA a relatively high risk of mortality and morbidity is associated also with elective AAA repair. The mortality and morbidity risks are obviously incomparably much higher in rAAA repair compared to elective repair. Symptomatic AAAs are associated with higher risk of morbidity and mortality compared to elective AAA repair, probably explained by the pre-rupture status that is suspected in symptomatic AAAs.^{77,79}

The outcomes of OR and EVAR for AAA have been extensively studied in different trials. The most well known randomized trials are the UK Endovascular Aneurysm Repair 1 (EVAR-1) trial, the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial and the Open versus Endovascular (OVER) trial, described below.¹¹⁰⁻¹¹² There is still no clear scientific evidence that favors long-term outcome results of one method over the other.¹¹³ An advantage for EVAR compared to OR has been suggested in the latest trials, especially in rAAA. However criticism has been raised towards design and patient selection in these trials.¹¹³ Theoretically EVAR could be advantageous in the rAAA patient group with hemodynamic and physiologic impairment as it is minimally invasive and can often be performed under local anesthesia.¹¹⁴

Several factors contribute to the outcome of repair for AAA. Age, comorbidity and medical history, ongoing and previous smoking, physical fitness and the anatomic complexity and morphology have been suggested as important factors for the outcome. The AAA morphology has been studied on CT and MRI and attempts have been made to suggest protocols for three-dimensional evaluation, however no consensus has been reached of how morphology relates to outcome.¹¹⁵

1.3.6.1 Elective Abdominal Aortic Aneurysms

Clinical trials evaluating outcome of AAA repair over the last 10 years have mostly focused on comparing EVAR to OR. In 2005 the EVAR-1 trial from UK compared OR to EVAR for

the treatment of AAA.¹¹⁶ A study from the Netherlands (DREAM trial) also presented a comparison between OR and EVAR.¹¹⁷ In 2009 the results from the OVER study from the USA presented their results comparing the two methods.¹¹⁸ The French ACE trial reported a comparison in 2011.¹¹⁹ A meta-analysis from 2013 included the above studies together with material from the Swedish Vascular registry and the Medicare registry from the USA to analyze short- and long-term outcome. There was an overall short-term survival advantage (30-day mortality) in patients treated with EVAR (EVAR 1.3% vs. OR 4.7%). The long-term survival in comparing the two methods showed no statistical difference. In the EVAR group fewer myocardial infarctions (MI) were seen, but this group instead had more re-interventions and ruptures. The rate of renal insufficiency and stroke were similar in the RCTs.¹²⁰

1.3.6.2 Symptomatic Abdominal Aortic Aneurysms

Mortality rates for symptomatic AAAs have been ranging from 4-22%. Morbidity in the symptomatic AAA is also higher than normal elective AAA repairs.^{77,78,121,122} The reasons for this are unknown but several factors probably contribute. The pre-rupture status has been mentioned as a strong contributing factor but does probably not fully explain the increased risks. Most of the deaths after repair of symptomatic AAA repair have been attributed to cardiac complications.¹²³ Morbidity has also been reported to be high and includes MI, stroke, respiratory and renal failure.¹²⁴ It has been suggested that unknown heart disease is more common in patients presenting with symptomatic or ruptured AAA than in elective AAA patients and hence without comparable cardio-protective therapy such as aspirin, beta-blockers and statins. This could contribute to increased risk.^{123,125,126}

1.3.6.3 Ruptured Abdominal Aortic Aneurysms

Ruptured AAAs are associated with dramatic presentations with possible hemodynamic shock, coagulopathy and associated high risk of mortality and morbidity. The associated mortality rates after rAAA repair have been reported to range from 20% to 50%.^{77,113,127-129} The most common complications reported are: respiratory failure, multi organ failure (MOF), MI, renal insufficiency, abdominal compartment syndrome (ACS), leg ischemia and bowel ischemia.^{77,130} Reduced mortality has been suggested to be associated with increased use of EVAR in high volume, teaching centers and weekday admission according to a study that compared outcome in USA and UK.¹³¹

Three RCTs (Nottingham, AJAX, and IMPROVE) have compared the outcome of OR vs. EVAR in patients with rAAA.¹³²⁻¹³⁴ The studies failed to show any significant difference in 30-day mortality [OR vs. EVAR; 53% vs. 53%, 25% vs. 21%, and 37 vs. 35% respectively]. Data from the RCTs on blood loss and transfusion are presented in section 2.7.

1.4 HEMOSTASIS

A basic understanding of hemostasis is fundamental in bleeding research. The hemostatic process is key to find new methods to tackle the potential dangers of bleeding in AAA repair.

1.4.1 Definition

The process of hemostasis acts as the bodies' defense mechanism against hemorrhage. The body has a remarkable ability to control bleeding if it occurs, given that it is not too extensive. Hemostasis is usually divided into primary and secondary hemostasis. It also includes the regulation of hemostasis. The processes occur at the same time and together. In primary hemostasis, vasoconstriction and platelet aggregation take place. In secondary hemostasis the blood coagulation system is activated. The regulatory mechanisms of hemostasis by fibrinolysis and other inhibitory systems are essential for the clot formation to occur at the right location in the body and to the appropriate extent.

1.4.2 The hemostatic process

1.4.2.1 Primary hemostasis

The endothelial cells in the vascular wall take part in regulation of the vascular tone. In the case of injury the smaller arteries constricts in order to divert blood from the damaged area. This is mediated by the release of vasoactive proteins from the damaged endothelial cells and from thromboxane A₂ (TXA₂) and serotonin released by activated platelets.

The extracellular matrix (ECM) in the subendothelial layer contains the highly reactive proteins collagen and von Willebrand factor (vWF). In the case of damage the exposed collagen and vWF bind to and **activates** the platelets and they start to stick to and roll on the vascular wall by **adhesion**. Eventually they slow down and stop and the platelets bind to each other causing **aggregation** and a platelet plug is formed.

When platelets are bound by their receptors to the ECM, thrombin will be generated and granules in the platelets will release adenosine diphosphate (ADP) and TXA₂. When platelets are activated and adhere to each other and the ECM, they change from their discoid shape to become spherical with dendritic structures protruding out from the body. This structural change together with activation of fibrinogen helps the aggregation.

The primary platelet aggregation is not stable enough on its own. It needs the fibrin matrix produced by the process of blood coagulation in order to firmly stabilize the clot. The initial thrombus formation of aggregated platelets will generate a phosphatidylserine-exposing membrane surface, which will cause the formation of tenase and prothrombinase complexes and activated coagulation factors.¹³⁵⁻¹³⁸ *Figure 5* describes the most important steps of platelet function in hemostasis.

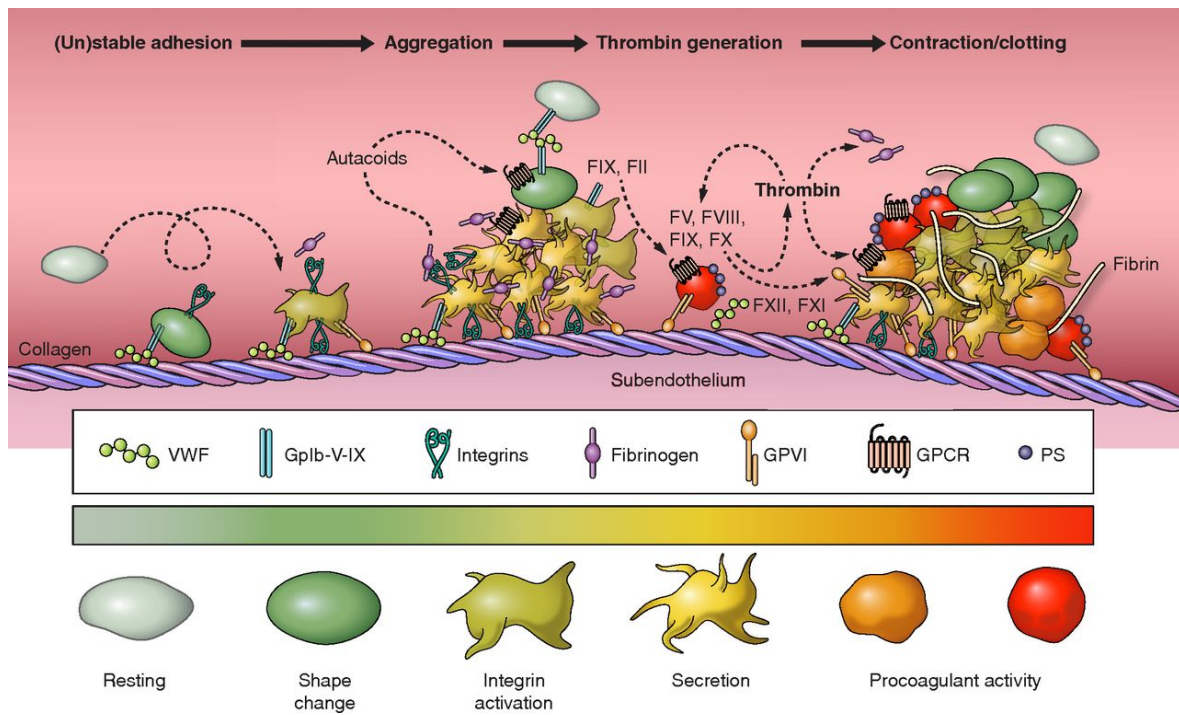


Figure 5. Platelet activation, adhesion and aggregation. The stages of platelet activation and thrombus formation. "Platelets adhere to von Willebrand factor (vWF)/collagen matrix, get activated, secrete granular contents, aggregate via integrins, produce thrombin after developing a procoagulant surface, and form a contracted thrombus with fibrin. Heat map with color codes from green (low Ca^{2+} signal) to red (high Ca^{2+} signal). Procoagulant platelets provide a phosphatidylserine (PS)-exposing surface for the tenase complex (activated FVIII and FIX) and the prothrombinase complex (activated FV and FX). Formed thrombin provides positive-feedback" From Versteeg et al.²¹ Used with permission from the publisher.

1.4.2.2 Secondary hemostasis

The process of coagulation is a complex set of events with activators and inhibitors that have been elucidated by many authors.^{21,26} It is often described as a set of chain reactions (frequently referred to as a cascade) and propagation loops where also positive and negative feedback loops play important parts. The aim of the coagulation process is to form enough fibrin matrix to form a strong and stable clot and heal the vascular wall.²¹

The coagulation cascade is **initiated** by TF released from fibroblasts, macrophages and endothelial cells after injury to the vessel wall. TF binds to activated FVII (FVIIa), which activates FIX and FX into FIXa and FXa. FXa activates FV and forms a complex (prothrombinase). These FXa/FVa complexes bind to TF and start to convert prothrombin to thrombin.²¹

Thrombin **amplifies** the coagulation process by activating more FV into FVa, FVIII into FVIIIa and FXI into FXIa. The platelets are hence further activated.

On the activated platelet complexes of FIXa/FVIIIa (tenase complex) and FXa/FVa **propagates** the coagulation further by converting masses of prothrombin into thrombin. The thrombin splits fibrinogen into fibrin monomers, which form the stable fibrin mesh together with the activated platelets.²¹ The above mechanisms are briefly illustrated in Figure 6. The fibrin mesh is visualized in Figure 7.

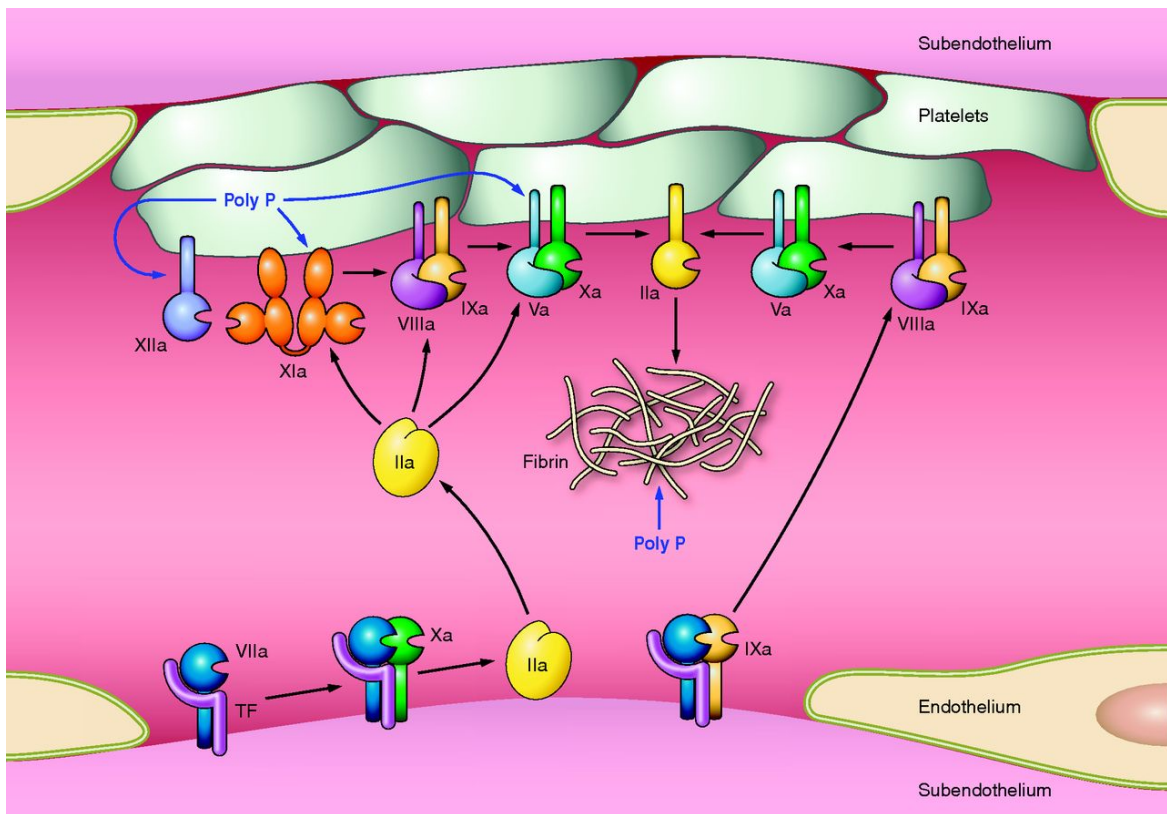


Figure 6. The coagulation cascade. "Upon endothelial damage, tissue factor (TF) is exposed to the bloodstream and binds factor VII, which is activated to factor VIIa. The TF:VIIa complex enables subsequent activation of factor X and prothrombin, after which small amounts of thrombin activate the factor XI-IX feedback loop on the platelet surface. Factor IXa will then activate additional factor X. Simultaneously, the trace amounts of thrombin will then activate factors VIII (cofactor to factor IX) and V (cofactor to factor X), which dramatically enhances catalytic activity of factors IX and X. Finally, thrombin (factor IIa) activation leads to fibrin deposition. In parallel, local polyphosphate (polyP) release by activated platelets may additionally stimulate activation of factor XII, factor V, and FXI and inhibit clot lysis." From Versteeg et al.²¹ Used with permission from the publisher.



Figure 7. Red blood cells trapped in fibrin threads. A stable fibrin mesh is formed. Thrombin (FII) converts Fibrinogen into Fibrin. The Fibrin form stable strands between the platelets and the other blood cells as demonstrated by the electron microscope picture. "red blood cell: red blood cells trapped by fibrin threads". Photograph. Encyclopædia Britannica Online. Web. 16 apr. 2015 Open access, with permission.

1.4.3 Regulation of hemostasis

The inhibitory regulation of coagulation by fibrinolysis and other mechanisms control the coagulation process and stop it when the goal of hemostasis is reached. These mechanisms are important contributors to the success of the coagulation system.²⁶

The inhibition is mediated by inhibitory enzymes and by modulation of the functions of the coagulation factors. The most important inhibitory enzymes are antithrombin, protein C and tissue factor pathway inhibitor (TFPI). In the normal vascular wall prostacyclin (PGI₂) and nitric oxide (NO) prevent platelet activation and aggregation.

Antithrombin is present in normal blood and inhibits several of the coagulation process' free enzymes thereby limiting the coagulation process to the site of injury. Protein C is activated into activated protein C (APC) by thrombin binding to thrombomodulin, a receptor on the endothelial cell. APC and its cofactor, protein S, inactivate FVa and FVIIIa thereby significantly decreasing the production of thrombin. Tissue factor pathway inhibitor (TFPI) regulates the initiation of the coagulation system by effectively inhibiting the TF/FVIIIa complexes and FXa. This shuts down the initial phase of plasma coagulation.

Fibrinolysis refers to the process of fibrin breakdown. Fibrinolysis is mediated through the conversion of plasminogen to plasmin by enzyme activators, tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). This process takes place after circulating plasminogen binds to a fibrin clot. T-PA is the most important of the plasminogen activators and is itself inhibited by plasminogen activator inhibitor-1 (PAI-1) and PAI-2, activated thrombin activatable fibrinolysis inhibitor (TAFIa) and α 2-Antiplasmin.¹³⁹

1.4.4 Effect of bleeding on hemostasis

Bleeding and vascular injury is the trigger of hemostasis. Large volume bleedings left untreated empties the supplies of blood cells and coagulation factors and leads to hampered hemostasis. Vasoconstriction compensates for the lost blood volume but implies also the loss of peripheral temperature control, which in turn eventually leads to a lower central temperature, and decreased ability of the hemostatic process to function.¹⁴⁰

1.4.5 Coagulopathy

1.4.5.1 Definition

Coagulopathy is defined as impaired hemostasis.¹⁴¹ No general consensus exist for laboratory threshold values or limits for impairment to define coagulopathy. Some authors also describe coagulopathy as a hypercoagulable and thrombotic state.¹⁴¹ In the following text coagulopathy is referred to as a defect ability to form a stable clot. It can be acquired by heavy bleeding, sepsis, trauma, hypothermia (<36.5°C), dilution, disease, narcotics use or through medication. Hemostatic disorders can also be inherited such as von Willebrand disease, coagulation factor or platelet disorders. Coagulopathy can lead to uncontrollable bleeding and if not properly treated it is associated with a significant risk of mortality.^{141,142}

1.4.5.2 Pathophysiology

Coagulopathy can develop either through deficiency or malfunction of platelets and coagulation factors, activators and enzymes. It can also develop due to an altered environment in which the hemostatic process does not function properly, such as hypothermia, acidosis, insufficient number of RBC ($<90\text{g/L}$) and low ionized Calcium (Ca^{2+}). Also the use of medications can alter coagulation and platelet function.¹⁴¹

Coagulopathy has been described to develop during lengthy surgery procedures, probably due to fibrinolytic activation, dilution, altered environment (as above) and unknown stress-related effects.¹⁴²

Trauma induced coagulopathy (TIC) or Acute Traumatic Coagulopathy (ATC) has been described as the rapidly observed malfunctioning of coagulation after major trauma.^{143,144} Threshold values for coagulopathy of PTr-INR >1.2 and APTT >35 s have been suggestive of coagulopathy.^{145,146} The role of viscoelastic testing (TEG/ROTEM) for developing new definitions is under way.¹⁴⁷

1.4.6 Medical drugs that alter hemostasis

A vast number of medical drugs have been developed to modify the coagulation process in order to avoid thromboembolic events that can lead to stroke or myocardial infarctions. Anticoagulants can be organized according to the inhibitory effect by which they act or by their molecular similarity.

Vitamin-K-antagonists (Warfarin) and Heparin, low molecular weight heparin (LMWH) and the new oral anticoagulants (NOACs) acts on the coagulation system by inhibiting different coagulation factors or feedback loops. These medications are given to inhibit thrombosis formation. Enzymes such as Alteplase and Streptokinase are used to enhance the fibrinolysis and dissolve a formed thrombus.

Antiplatelet drugs are among the most commonly prescribed medicines due to their protective effects for myocardial infarction. The most common antiplatelet drugs are Acetylsalicylic Acid (ASA), Clopidogrel, Prasugrel and Ticagrelol. ASA inhibits COX-1 from binding to TXA_2 receptor whereas Clopidogrel, Prasugrel and Ticagrelol inhibit the ADP-P2Y_{12} receptor on the platelets. The even more aggressive platelet inhibitory drugs Acciximab, Tirofiban and Eptifibatide are GPIIb/IIIa receptor inhibitors.¹⁴⁸

Also other medications, such as steroids (prednisolone, cortisone), non-steroid anti-inflammatory drugs (NSAID) (ibuprofen, diklofenac) and anti-depressive serotonin inhibitors are known to interfere with coagulation and increase risk of bleeding.¹⁴⁹

1.4.7 Measuring hemostasis

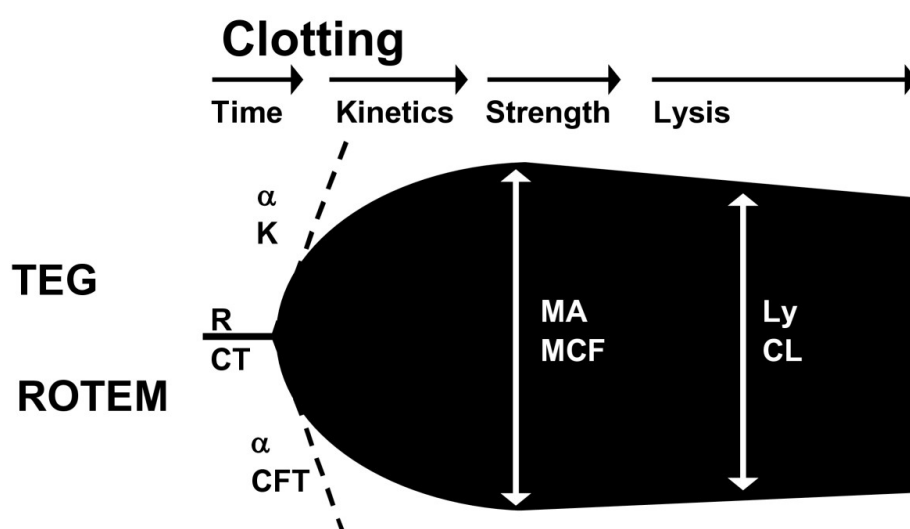
The functionality of the hemostatic process can be measured by a number of different laboratory tests and methods presented in *Table 1*.

Table 1. *Tests for hemostasis*

Test name and units	Method	Description of test	Reference interval
Platelet concentration (10 ⁹ /L)	Platelet count by automated impedance or flow-cytometric quantification	Measures the platelet number but not function	125-400 (10 ⁹ /L)
Activated partial thrombin time APTT (s)	Clotting time in plasma after adding reactant	Activity of factors II, V, VII, IX, X, XI, XII and fibrinogen, usually used for measuring affect of heparins	30-40 s (depends on the type of the reactants used, no international standard exists)
Anti-FXa activity	Specific calibration to each of medications tested	Concentration of heparin and LMWH, rivaroxaban apixaban, fondaparinux	According to local laboratory
Prothrombin time ratio-International Normalized Ratio PTr-INR (ratio)	Coagulation time Measured in reactant (thromboplastin, FV and fibrinogen) only measuring K-vitamin dependent F II, VII and X	Warfarin effect test standardized by relating local protrombin time to international standard	<1.2 (normal). The suggested therapeutic interval for patients on warfarin is usually suggested to (2.0-3.0).
Prothrombin time PT (s)	Time for plasma to form a clot after addition of TF	High variance therefore replaced by PTr-INR	11 - 13.5 s
Activated clotting time ACT (s)	Time for clot to form in whole blood after adding FXII activators	Affected by several factors, normally used as bedside test of heparin effect as it is very quick	107 ± 13 s
Fibrinogen (g/L)	Clauss method Adding excess amount of thrombin	Estimates Fibrinogen concentration	>2-4 g/L
P-Antithrombin (units depend on test method)	Measures heparin cofactor activity, different techniques are available	Low values are seen in massive bleeding due to consumption of coagulation factors and in liver deficiency and long term Heparin use	80 - 120 % of expected value
TEG and ROTEM	Clot formation activation by Kaolin or TF	Thromboelastogram acquired by clot formation time and strength and durability by mechanic evaluation	See Figure 8

Different platelet function test; Multiplate, VerifyNow, PFA-100 ¹⁴⁸	Analysis of platelet function by assessing receptor reactivity in a variety of methods	Platelet function testing	
pH	Assessing acidity		>7.2
Ca ²⁺ (mmol/L)	Concentration of Ionized Calcium by using an ion selective potentiometric electrode	Ionized Calcium is the most secure form of measuring active Calcium concentration in blood	1.14 – 1.32
Temp (°C)	Central body temperature should be used	Low body temperature impair hemostasis	>36.5

A brief description of viscoelastic tests of hemostasis is presented in *Figure 8*.



*Figure 8. A sample trace of the viscoelastic tests of TEG and ROTEM is demonstrated; **R/CT** (reaction/clotting time) measures the speed to reach a specific level of clot strength, **α** -measures the rate of clot formation and reflects the rate of fibrin build up, **MA/MCF** (maximum amplitude/maximum clot firmness) represents the strength of the clot (platelets & fibrin) function of maximum dynamic properties of fibrin & platelet bonding via GPIIb/IIIa receptors **LY 30/CLI** (lysis at 30 minutes as ratio of MA/clot lysis index) measures clot stability by rate of amplitude reduction from MA at 30 minutes, detects fibrinolysis.¹⁵⁰ Used with permission from the publisher (Open Access article).¹⁵¹*

1.5 BLEEDING

Surgical bleeding can be referred to as either perioperative or postoperative bleeding. In this thesis perioperative bleeding is the main focus. Other types of bleeding can occur, induced by medical drugs altering the hemostasis balance, due to disease, trauma or unknown/spontaneous bleeding. The specific considerations related to bleeding in AAA will be described in section 1.7.

1.5.1 Monitoring and measuring bleeding

It is difficult to accurately measure perioperative blood loss. Literature describes that the surgeon often underestimates the blood loss. Therefore the anesthesiologist in charge often estimates the blood loss by adding several factors.¹⁵² First the blood collected in operative gauzes and suction from the wound is measured. To this is added an estimation of the bleeding volume based on resuscitation and transfusion requirements, hemodynamic status and hemoglobin. It is argued in the literature that the patients' normal physiology and estimated total blood volume should also be taken into account when calculating perioperative blood loss. Formulas for calculating perioperative blood loss have been suggested.¹⁵²

1.5.2 Patient reactions to bleeding

Patients react to perioperative bleedings differently according to preoperative physiologic status such as previous cardiovascular diseases, and general health and fitness. The magnitude of bleeding will affect the patient in different ways. The classification described by Baskett of bleeding volumes related to the patients estimated blood volume is widely used in trauma literature.^{153,154} It describes how different bleeding volumes, in healthy young males, in trauma, influence the hemodynamic status. The clinical relevance of this classification has however not been analyzed. The applicability of this classification in other settings than trauma can also be questioned. In the papers presented in this thesis we have not used this classification. It is included here for completeness of background and as a reference for the hemodynamic changes observed and related to bleeding. The volumes described below are related to an estimated blood volume (EBV) 5000 ml (as such of a 70 kg healthy male).

- | | |
|-----------|--|
| Stage I. | Loss of < 15% of the EBV (<750 ml)
No physiologic changes observed. Vasoconstriction maintains the blood pressure. |
| Stage II. | Loss of 15-30% of the EBV (750-1500 ml)
Patients react with tachycardia and possibly with a slight decrease in blood pressure. Blood flow is reduced to skin, muscles and abdominal organs, while the circulation to the heart and brain is maintained. |

- Stage III. Loss of 30-40% of EBV (1500 – 2000 ml)
Tachycardia and tachypnea compensates for a decreased cardiac stroke volume but normal circulation cannot be maintained and a significant reduction of blood pressure is observed. The patient is usually mentally affected.
- Stage IV. Loss of >40% of EBV (>2000 ml)
A significant increased risk for irreversible shock and death is observed if not the patient is resuscitated immediately. Blood loss of >50% EBV often results in unconsciousness and severe hypotension.

1.5.3 Treatment of bleeding

The treatment of bleeding, other than stopping it surgically, is constituted of blood volume replacement by intravenous fluids and blood transfusion. Intravenous fluids such as Crystalloids are given according to local protocol. If blood transfusion is necessary, Red Blood Cells (RBC) are given first and if the bleeding is significant, Plasma and Platelets are also transfused. A number of other measures can also be added to the treatment. If needed the patient is rewarmed, pursuing a temperature above 36,5 degrees Celsius, and by tribonate infusion a normal pH level is aimed for, as the coagulation system does not function properly in hypothermia and acidosis (pH <7,2). Extra coagulation factors, apart from the ones included in the transfusion of plasma, can be administered. Also other procoagulatory substances such as vWF and FVIII enhancers, Calcium and antifibrinolytic substances such as Tranexamic acid are frequently given in substantial bleeding.^{155,156} Cardiac stimulating and vasoactive drugs such as norepinephrine are also used if blood pressure deteriorates.

1.6 BLOOD TRANSFUSION

A number of inherent problems with blood transfusion must be overcome in order to minimize risks of serious complications. Blood is composed of plasma and blood cells. The red blood cells transport oxygen and carbon dioxide to and from the cells of the body. The white blood cells are important in the defense against infection and in inflammation. The platelets are the smallest blood cells and have numerous functions as mediators and as active participants in hemostasis and wound healing. Plasma contains much of the vital proteins. The coagulation factors are present in plasma.

The A and B antigens on the surface of the red blood cells and the anti-A and anti-B antibodies in plasma are the main obstacles to blood transfusion causing aggressive reactions if blood is transfused to a non-compatible blood group. The four blood groups A, B, AB and O are based on these antigens and antibodies. The Rhesus group system divides persons who are D-antigen carriers into positive (+) *present* and those without D-antigen as negative (-) *absent*. There are also minor systems for controlling compatibility of blood groups based on the presence of other antibodies (eg. Kell). Computerized and/or serological cross-matches should be performed before transfusion is initiated. In case of emergency when there is no time for cross matching only O(-) blood is transfused as this blood group can be universally donated.

Much of today's knowledge and practice of massive transfusion including the use of protocols are derived from the trauma literature.¹⁵⁷

1.6.1 Definition

Blood transfusion is defined as administration of blood components from one or more donors into the blood system of another patient. The compatibility of the donor vs. receiver must be known. Autotransfusion is defined as a process where a patient is transfused with his or her own blood.

1.6.2 Blood products

Transfusion of whole blood has again gained interest in combat zones from one warrior to another as a means of effectively using resources and decreasing the demands for advanced forms of collecting, storing and preparing blood products in remote areas.¹⁵⁸ The use of whole blood also has theoretical advantages compared the use of processed blood products described below. In order to make it possible to store and safely administer blood, it is usually collected and prepared by rigorously controlled methods.¹⁵⁹

Blood is collected and separated into units to be able to administer the products on demand i.e RBC for anemia, PLT to patients with thrombocytopenia and plasma to patients suffering from liver disease. In the case of substantial bleeding all of the components are required to replace the blood loss.

1.6.2.1 Red blood cells

In Sweden packed red blood cells are collected and stored in units of 210-300 ml containing red blood cells 120-200 ml, plasma 10-20 ml and nutritional solution (usually SAGMAN; *Saline, Adenine, Glucose and Mannitol*) \approx 100 ml. The units can be stored for up to 35-42 days in 2-6 °C. The RBCs are usually filtered for leucocytes.

1.6.2.2 Plasma

Plasma is prepared and stored in units of 210-280 ml. Fresh plasma can be stored in 2-6 °C for up to 14 days if coagulation factors VIII and V are reduced. Fresh frozen plasma (FFP) is frozen 8-18 h after collection and contains 70% of the normal amount of coagulation factors. One unit is prepared from a single donor. It takes about 30-45 minutes to thaw a unit of plasma. Thawed FFP is good for use for up to 5 days after thawing. In Sweden plasma from males only are used in order to avoid Transfusion Related Acute Lung Injury (TRALI).^{159,160}

1.6.2.3 Platelets

In Sweden one unit of platelets contains $>240 \times 10^9$ platelets extracted from 4-6 donors by centrifugation or apheresis. The platelets are suspended into 350 ml nutritional solution and leucocyte reduced plasma. The packed units of platelets are stored at 22 °C under continuous gentle agitation in plasticized bags for up to five days. In many other countries platelets are prepared and stored in units from a single donor. This implies that units of platelets referred to in international literature are composed of approximately 1/4th of the *Swedish* units.

1.6.3 Massive Transfusion

1.6.3.1 Definition

The most common definition of massive transfusion (MT) is transfusion of ≥ 10 units of RBC in 24 h.¹⁶¹ Alternative definitions are ≥ 4 u of RBC within 1 h and transfusion of 50% of the estimated blood volume in 3 h.¹⁵⁷ It might be argued that the former two definitions are advantageous because of the lesser timespan that has to be reached before declaring massive transfusion. However the first definition is by far the most widely used in the literature.¹⁵⁷

1.6.3.2 Massive transfusion protocol

Most emergency hospitals nowadays have a massive transfusion protocol (MTP). It should be well known and implemented as standard practice for the treatment of massively bleeding patients. The transfusion routines, including blood product ratios (RBC:FFP:PLT), should be stated in the MTP. It should also include the indications for use of pro-coagulatory drugs (i.e Fibrinogen and Tranexamic acid), Calcium and in need Tribonate. The MTP usually also includes suggested intervals and target values for blood chemistry analysis, temperature and blood pressure.^{157,162}

1.6.3.3 Autotransfusion

Autotransfusion is used as a method of perioperative blood salvage by collecting shed blood during surgery by suction into a device (e.g. Cell Saver[®] or other) and then giving it back to the patient. In the process of collection the automated system withdraws most of the plasma and platelets from the blood given back. By depletion of coagulation factors the autotransfused blood has lower risk of initiating an unwanted coagulation process.

Blood can also be collected from the patient in advance of a surgical procedure or treatment and stored and given back to the patient by transfusion if needed.

1.7 HEMOSTASIS, BLEEDING, COAGULOPATHY AND TRANSFUSION IN AAA

The repair of elective, symptomatic and ruptured AAA addresses special aspects on bleeding, hemostasis, coagulopathy and blood transfusion. The method of repair (OR or EVAR) impacts the way to approach these problems.

AAA disease itself may affect the hemostatic process.¹⁶³ The AAA patient might be on medications, which interfere with the hemostasis. In ruptured AAA, coagulopathy is reported to develop early.

Bleeding in aortic repair can be substantial and the surgical team including the anesthesiologist, coagulation laboratory and the blood bank must have a prepared strategy to deal with massive bleeding in these cases.

1.7.1 Hemostasis in AAA

1.7.1.1 AAA and hemostasis

Hypercoagulability has been suggested as a reason for thrombus formation in the vascular wall of an aortic aneurysm.¹¹⁷ It has been shown that patients with AAA have increased levels of fibrinogen, which might be a result of an ongoing inflammatory process.^{164,165} This might contribute to the activation of the coagulation. Hyperfibrinolysis and increased proteolytic activity have also been observed.¹⁶³ The formation of intraluminal thrombus at the site of the AAA has also been suggested to depend upon platelet activation and shear stress.^{166,167} A recent meta-analysis showed increased levels of fibrinogen, D-dimer and thrombin-antithrombin III complexes in plasma of AAA patients.¹⁶³

The risk of increased bleeding is one aspect of a malfunctioning hemostatic equilibrium in AAA repair. Perioperative and postoperative thrombus formation is another, sometimes with high morbidity and mortality as a consequence.¹⁶⁸

Additional studies are needed in order to answer if AAA is associated with imposed hypercoagulability or an inherent susceptibility to coagulopathy.

1.7.1.2 Coagulopathy in AAA

As stated above, many times coagulopathy develops early after rAAA and derangements in fibrinogen, PTr-INR, APTT and platelet count are frequently observed.¹⁶⁹⁻¹⁷² The exact frequency of coagulopathy in elective AAA repair is unknown and depends on the definition. Studies suggest that coagulopathy develops in rAAA patients because of the massive bleeding and the inflammatory response.¹⁷¹⁻¹⁷⁴

The existing definition of coagulopathy as malfunctioning hemostasis is very broad and therefore offers limited applicability in suggestions for treatment to correct coagulopathy. In AAA a detailed approach must guide the actions to be taken in order to correct the problems.

Transfusion policies where FFP and PLT are given in 1:1 ratios to RBC seem to counteract coagulopathy according to trauma literature.^{175,176} Further research is needed to investigate how different strategies of transfusion affect coagulopathy and how this applies to repair of AAA.

1.7.1.3 Measuring hemostasis in AAA repair

The commonly used tests to measure aspects of hemostasis are imprecise in validating the functionality of the hemostatic system.¹⁷⁷ The point-of-care tests using viscoelastic methods to measure thrombus formation (eg. TEG and ROTEM) are gaining popularity and might after further evaluations become gold standard.^{151,177}

Activated clotting time (ACT) is a bedside test that primarily measures the effect of heparin. However it offers a test complement to use also in evaluating coagulopathy.¹⁷⁷ ACT is commonly used as verification of the given heparin in cardiac, vascular and endovascular surgery.¹⁶⁸ In EVAR the goal ACT is 200-250 s to ensure a low risk of thrombotic complications. Boluses of heparin are given intravenously to maintain an adequate ACT.

To assess the functionality of platelets a variety of specific tests are available. TEG/ROTEM have previously been criticized for being insensitive for platelet dysfunction.¹⁷⁷ The most common specific platelet function tests are presented in *Table 1*.

Most of the tests described in *Table 1* offer specific measurements of individual parts of the hemostasis and will probably remain important in pinpointing specific deficits and weak spots in the hemostatic process.

The different methods of repair and also the acuteness of the AAA repair put different requisites to the measurements of hemostasis. To early detect a hypercoagulable state is just as important as identifying coagulopathy.

The perfect, quick, reliable, accurate, easy to use and cheap bedside test for assessing all parts of the hemostasis adapted to the demands of AAA repair is not yet identified.

1.7.1.4 Anti-coagulation medicines in AAA repair

According to a large retrospective material including 5527 patients undergoing elective AAA repair, 8% of the patients were on anticoagulation medicine or had bleeding disorders preoperatively.¹⁷⁸ It is common practice that patients on warfarin are advised to discontinue or alter their medication to LMWH before elective AAA repair.

In elective vascular surgery thrombotic prophylaxis is routinely given pre- and postoperatively in the form of LMWH. Different regimes exist but commonly LMWH is given subcutaneously 4-8 h postoperatively for one week or more in order to reduce the risk of postoperative deep venous thrombosis. Also during surgery anticoagulatory measures are taken by intravenous (IV) administering Heparin as a bolus dose of 5000 U (or individualized to patient approx. 70-100 IU/kg) before clamping the aorta or introducing large diameter

sheaths into the vessels during EVAR to reduce the risk of perioperative thrombosis. A survey from 1994 explored the use of Heparin among vascular surgeons in the USA and Europe.¹⁷⁹ An aggressive use of Heparin and reversal with Protamine was described. A recent survey study in UK reports that 95% of surgeons use IV Heparin in open AAA repair and 85% in AAA repair by EVAR.¹⁸⁰ ACT measures the effect as described above. During rAAA the same measures are usually not performed as coagulation deficiency is expected due to the bleeding. According to a recent review there is however no scientific evidence that supports not giving heparin also in rAAA for both OR and EVAR.¹⁶⁸

Some patients presenting with rAAA might be on continuous anticoagulation medication. The most common is warfarin but new oral medications (NOACs- new oral anticoagulants) are gaining popularity. Some of the new anticoagulants (e.g. the FX inhibitors) are lacking antidotes, which could cause serious bleeding problems in an emergency surgery situation. Warfarin can be reversed by vitamin K, plasma or more rapidly by prothrombin complex concentrate (PCC). The effect of heparin and LMWH can be reversed by protamine.¹⁵⁵

1.7.1.5 Platelet inhibition in abdominal aortic aneurysm repair

In elective AAA repair patients on antiplatelet medication are usually kept on their medicine as secondary prophylaxis in order to reduce the risk of myocardial infarction and stroke. The prevalence of AAA patients on ASA differs in literature 13-49%.^{65,67} A prevalence of >50% cardiac comorbidity is frequently reported.¹⁸¹ In the ADAM screening study for AAA a comorbidity of atherosclerosis was reported in 36%.⁶⁷ No randomized trials investigate the benefit of platelet inhibition in AAA patients. A meta-analysis from 2002 suggests that patients with known arterial occlusive disease have a yearly 25% risk reduction for cardiovascular event if on long-term antiplatelet medication.¹⁸² ASA is the most commonly used antiplatelet medicine followed by Clopidogrel. Modern antiplatelet drugs such as Ticagrelor are becoming more common and we might expect that they will be more frequently used also in patients with known or unknown AAA. In perioperative hemostasis this can become a problem if emergent surgery is needed considering the long half-life and the profound effect that the modern drugs imposes on platelet function.

Patients presenting with rAAA might be on platelet inhibitory drugs. No antidotes are available to these drugs. The only way to increase the platelet functionality is to transfuse platelets. In patients on Ticagrelor several platelet transfusions can be required, as active medicine still is present in the blood.

1.7.2 Bleeding in AAA repair

1.7.2.1 Method of repair

1.7.2.1.1 Elective AAA

Open AAA repair has always been considered to be associated with a high risk of large volume bleeding. Thorough preparation and meticulous operative technique can reduce the

perioperative blood loss but, but as it seems in comparative literature OR vs. EVAR, only to a certain extent in low risk elective patients.¹⁷⁸

According to two randomized controlled trials (RCT) comparing elective OR and EVAR the perioperative bleeding in OR ranges between 1000-1500 ml compared to EVAR with substantially lower perioperative bleeding volumes of 200-400 ml.^{111,112,183}

1.7.2.1.2 Ruptured AAA

Also in ruptured AAA patients, different bleeding volumes are reported according to method of repair. In EVAR patients the mean blood loss for rAAA range from 200 ml to 1100 ml and in OR patients it ranges from 2000-4500 ml according to a review from 2007.¹⁸⁴ Out of the three randomized controlled trials (Nottingham, AJAX and IMPROVE trials) comparing OR and EVAR for rAAA the two first reported significant difference in perioperative blood transfusion.¹³²⁻¹³⁴ The IMPROVE trial did not report blood loss or transfusion. Other rAAA studies have showed decreased bleeding volumes and transfusion requirements for EVAR.^{132,185,186} Transfusion volumes in EVAR vs. OR for rAAA patients were reported to range between mean (units) of 0-3.78 and 6-10.7 respectively in a review.¹⁸⁴

1.7.2.2 Perioperative bleeding

Bleeding is a feared complication to elective AAA surgery. Large volume bleeding in open AAA repair can occur during the procedure due to iatrogenic injuries to arteries and veins during dissection and the rest of the course of the surgery. Brisk back bleeding from lumbar arteries or the inferior mesenteric artery after opening the aneurysm sac can also be encountered. Bleeding can also occur when failing to obtain adequate proximal and distal control over the aorta and iliac or femoral arteries. The trauma of the surgical procedure and the added bleedings during the surgery can also induce coagulopathy.

In EVAR for elective AAA the most frequent cause of perioperative bleeding is the failure to ensure adequate sealing and closure of the femoral access sites during and directly after the procedure. Introducers of varying diameter sizes are used to deliver the endovascular grafts necessary for repair. In the changing of introducers bleeding can occur. The access sites must be securely closed after completing the aortic repair. This can be achieved using different methods such as open raphie of the artery, closure devices and as studied in Paper I, the fascia suture technique. The failure to adequately close the femoral access sites can lead to significant perioperative and postoperative bleedings.

In rAAA significant bleeding many times starts and continues from the time of the rupture. The aorta is located in the retroperitoneal space, in many cases the bleeding after the initial AAA rupture and is contained to a limited space in the retroperitoneum. *See Figure 9.* A free intraabdominal aortic wall rupture would inevitably lead to the rapid emptying of the patients' blood volume. The containment of the bleeding after rupture leaves a treatment window of opportunity before the containment finally bursts into the abdominal cavity. The

length of the treatment window is not well known and varies due to the physiologic uniqueness of each patient.^{65,128}

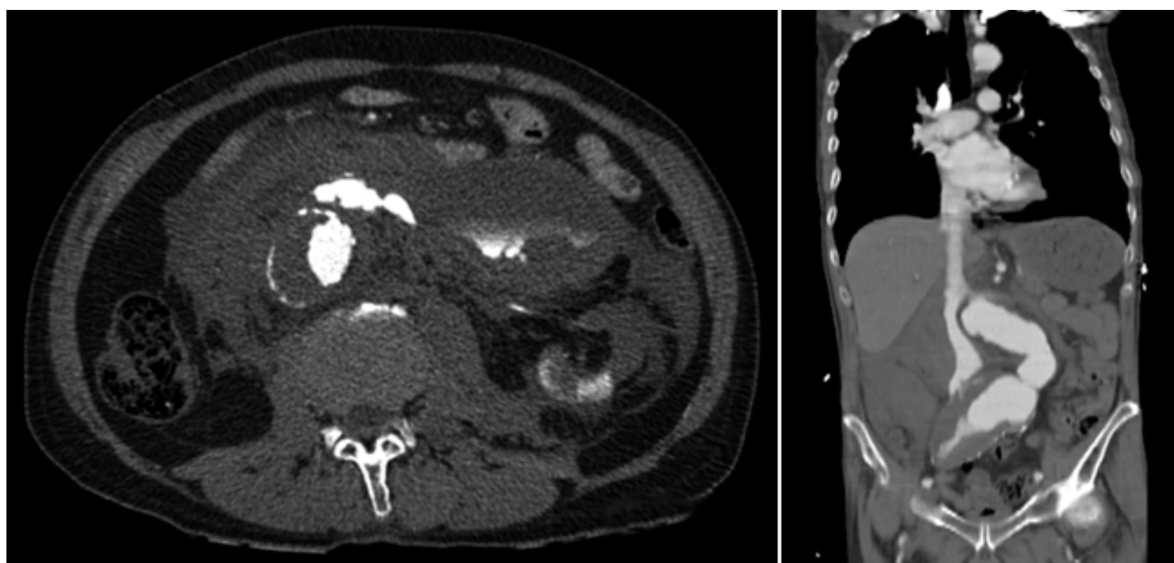


Figure 9. Computer tomography angiogram of a ruptured abdominal aortic aneurysm with a large retroperitoneal hematoma

1.7.2.3 Postoperative bleeding

Postoperative bleeding is defined as bleeding that takes place in the postoperative period. After open repair postoperative bleeding can be caused by anastomotic leakage, iatrogenic injuries and coagulopathy induced during and/or after the surgery. Postoperative bleeding after EVAR usually occur from the femoral access sites but can also be caused by endoleakage, iatrogenic injury to the aorta, the iliac arteries and other vessels.

After repair of rAAA, postoperative coagulopathy is a known risk for postoperative bleedings. Postoperative bleeding is suggested as one explanation to abdominal compartment syndrome in both OR and EVAR after rAAA.^{187,188}

1.7.3 Blood transfusion in AAA repair

1.7.3.1 Transfusion in AAA patients

Scientific evidence from studies of massive bleeding in trauma and other fields suggests replacing blood loss by transfusing patients with blood products that resembles the constitution of whole blood as much as possible.^{175,189} The RBC:FFP ratio has been shown to impact survival in trauma patients with massive hemorrhage.¹⁷⁵ The latest guidelines describe evidence supporting using ratios of 1:1:1 RBC:FFP:PLT and early administration of coagulation factors.¹⁹⁰ It is a general practice that these should be applied to all patients requiring MT.¹⁵⁷ In AAA repair it has not been proven that a strict coherence to transfusions guidelines is beneficial for the outcome of these patients.

The optimal hemostatic resuscitation of patients with rAAA undergoing OR or EVAR has not been well defined. EVAR in rAAA has been described to be associated with decreased

bleeding volumes and transfusion requirements.^{132,185,186} In aortic surgery only a few studies have tried to investigate transfusion regimes.^{191,192} No randomized control study exists. As ruptured open repair AAA patients often require MT, this group offers a potential study population to further develop the optimal transfusion strategy for this patient category.

According to a report from Mann et al 2011, the routine of cross-matching blood preoperative to elective EVAR is unnecessary. In a series of 203 consecutive EVAR cases only 3 patients required massive transfusion. Only 6 % of the patients required any transfusion.¹⁹³

1.7.3.2 Transfusion recommendations in ruptured AAA patients of today

It might be suggested that the massive hemorrhage observed in rAAA patients calls for coherence to the existing massive transfusion guidelines also in these patients. Only a few previous studies have evaluated blood transfusion in patients undergoing rAAA repair. In 2010 Mell et al. reported reduced mortality in patients receiving an equivalent ratio of FFP and RBC and also concluded an advantage to early plasma transfusion in rAAA patients.¹⁹² In 2007 Johansson et al. reported that proactive administration of platelets and FFP has positive effects on coagulation and survival.¹⁹⁴

The optimal transfusion strategy in rAAA has not been completely investigated.

1.7.4 Summary

The repair of AAA benefits from a thorough understanding of problems related to hemostasis, coagulopathy, bleeding, and blood transfusion. A structured workup with regard to increased risk for bleeding with patient history, medications, and preoperative coagulation tests should be the standard procedure before AAA repair regardless the method.⁸²

Preparedness in the surgical team and close collaboration with the blood bank and coagulation laboratory is important in order to provide quick and adequate response in case of major bleeding in rAAA repair. Endovascular repair has decreased the need of transfusion in elective end emergency repair of AAA.

2 AIMS OF THE THESIS

The overall aim of this thesis was to investigate the clinical problem of bleeding in open and endovascular repair in both ruptured and elective abdominal aortic aneurysms. Aspects on bleeding and association to risk factors and outcome in this patient group were studied.

In the four studies the following specific aims were addressed:

- To investigate if the fascia suture technique for femoral access site closure after EVAR is a safe method for obtaining perioperative hemostasis and vascular closure and if risk factors for failure of the method could be identified.
- To evaluate the outcome and predisposing factors related to perioperative bleeding in patients treated with endovascular aneurysm repair for ruptured and non-ruptured abdominal aortic aneurysms.
- To investigate coagulation laboratory tests and their association to preoperative hemodynamic status, perioperative bleeding and outcome in patients undergoing repair for ruptured abdominal aortic aneurysms.
- To study the effect of blood transfusion and blood product ratios on outcome in massively transfused patients treated for ruptured abdominal aortic aneurysms.

3 PATIENTS AND METHODS

3.1 STUDY DESIGN PAPERS I-IV

In these studies the subjects were primarily identified through local or national vascular registries and matched with the local computerized medical records and databases by their Swedish personal identification number.

The Swedish Vascular Registry (Swedvasc) was used in Studies II-IV. The Swedvasc is continuously matched to the national mortality registry thereby providing automated update of mortality.

The local laboratory database at Karolinska University Hospital was used in Study II and III.

The regional transfusion registries of Skåne University Hospital and the Stockholm Region were used in Study IV.

Table 2 shows a summary of the patients, methods, study designs and centers used in the Studies I-IV.

Table 2 *Overview of study designs, patients, methods and centers involved*

	Patients and materials	Study design and methods	Centers
Study I	100 consecutive patients undergoing elective or emergent EVAR 2007-2008	Retrospective follow-up study of fascia suture technique, results and preoperative risk factors for failure	Dept. of Vascular Surg. Skåne University Hospital
Study II	525 consecutive patients treated with elective or emergent EVAR 2008-2011	Retrospective study of perioperative bleeding and the effect on outcome	Dept. Vascular Surg. Karolinska and Skåne University Hospital
Study III	91 consecutive patients treated for ruptured AAA by open repair or EVAR 2008-2013	Study of preoperative coagulation tests and the relationship to bleeding and outcome	Dept. Vascular Surg. Karolinska
Study IV	369 rAAA patients undergoing open repair or EVAR 2008-2013	Retrospective analysis of transfusion ratios and timing in massively transfused patients	Dept. Vascular Surg. Karolinska, Skåne University Hospital and Södersjukhuset

3.2 ETHICAL CONSIDERATIONS

3.2.1 Ethical considerations Paper I

Paper I was a quality assurance study of a newly introduced surgical method (FST) for closing the femoral access site after EVAR. According to the Malmö University Hospital practice in similar cases no application to the local ethics committee was needed in order to conduct this follow-up study. The patients studied were unaware of this newly implemented method of closure that was, earlier, reported as safe and associated with few complications.¹⁹⁵

The alternatives to FST before introduction of the method, was surgical cut down and lateral arteriography or suture mediated closure devices (double ProStarXL®). Surgical cut down is known to be a safe method, however associated with a considerable risk of complications such as perioperative and postoperative bleeding, infection and lymphatic leakage. According to a systematic review of 13 EVAR studies performed with surgical cut down the local wound complication rate varied from 2-26%.¹⁹⁶

The use of suture mediated closure devices such as the double ProStarXL® was at this time used outside the instructions for use provided by the company. The method has been previously studied and shown to be safe and associated with acceptable risks of complications.¹⁰⁸ The double ProStarXL® method however also have, disadvantages such as cost and prolongation of the surgical procedure, which poses possible problems especially in rAAA patients where a speedy procedure is of vital importance. A failure rate of 2%-10 % has been described.¹⁰⁷

There was an apparent need of an alternative method for simplifying closure of the femoral access sites after EVAR at the time of the implementation of the FST. The study did not imply deviation from the normal practice of follow-up or other aspects of treatment not related to the closure of the femoral access sites, for the patients.

3.2.2 Ethical considerations Paper II-IV

The regional ethics committee in Stockholm approved studies II-IV (reference number 2011/664-31/3). The retrospective nature of these studies meant no deviation from normal treatment or follow-up. All data was collected from registries, data banks and computerized medical records all of which previously has been under thorough investigation concerning the ethical aspects of data management and usage. The studies were performed according to Declaration of Helsinki and the Karolinska Institutets guidelines for good ethical practice.¹⁹⁷ The data banks were anonymized and kept secured from unauthorized use.

3.3 PATIENTS AND METHODS PAPER I

In this study the aim was to evaluate the efficacy, safety and preoperative risk factors for failure of the fascia suture technique (FST), previously described by Dietrich 1997.¹⁹⁸ It was a retrospective study of 100 consecutive EVAR patients at a tertiary high volume vascular surgery center.

3.3.1 Inclusion

The new method of FST for closing of the femoral access sites after EVAR was introduced at Malmö Vascular Center in 2007. It was decided that the technique should be used as the first hand method by all surgeons performing EVAR. Data was collected prospectively and analyzed retrospectively in order to evaluate the method with regard to success, safety and outcome. Clinical examination and CTA was included at 30-day and 1-year follow-ups within the analysis. It was decided to consider 100 consecutive EVAR patients for inclusion in the study. Patients were enrolled during the study period of 1 March 2007 until 21 April 2008. See *Figure 10*.

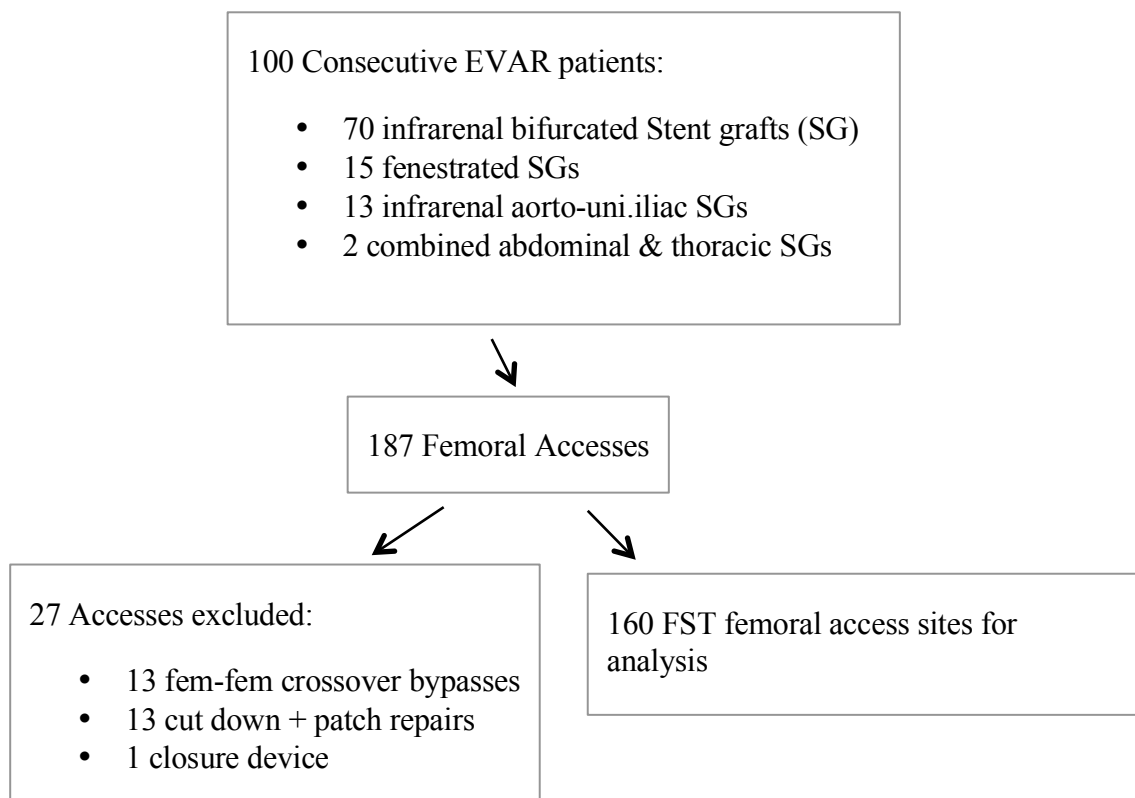


Figure 10. The flow chart illustrates the study material

In the 100 consecutive patients a total of 187 femoral access sites were used. In 160 of these FST was the primary method of closure. These access sites comprised the study material. A number of 27 access sites were excluded as they were primarily chosen for open access and closure by raphie or patch closure. One case was closed with closure device.

3.3.2 Pre- and postoperative imaging

The patients preoperatively underwent a CTA of the aorta and femoral access sites for planning of the EVAR procedure. The pre- and postoperative follow-up CTAs (1-month and 1-year) performed at other centers were sent to Malmö Vascular Center for evaluation.

3.3.3 Risk factor and grade of stenosis assessment by computer tomography

3.3.3.1 The puncture site

As the exact location of the puncture site was unavailable both before and after the EVAR, the puncture site on CTA was assumed to be located on the mid part of the common femoral artery between the epigastric artery and the femoral bifurcation. All measurements were calculated as mean values of three individual measurements, at 5 mm intervals, at the assumed site of the arterial puncture.

Figure 11 describes the measurements and evaluation of the CTA with regard to studied risk factors and grade of stenosis.

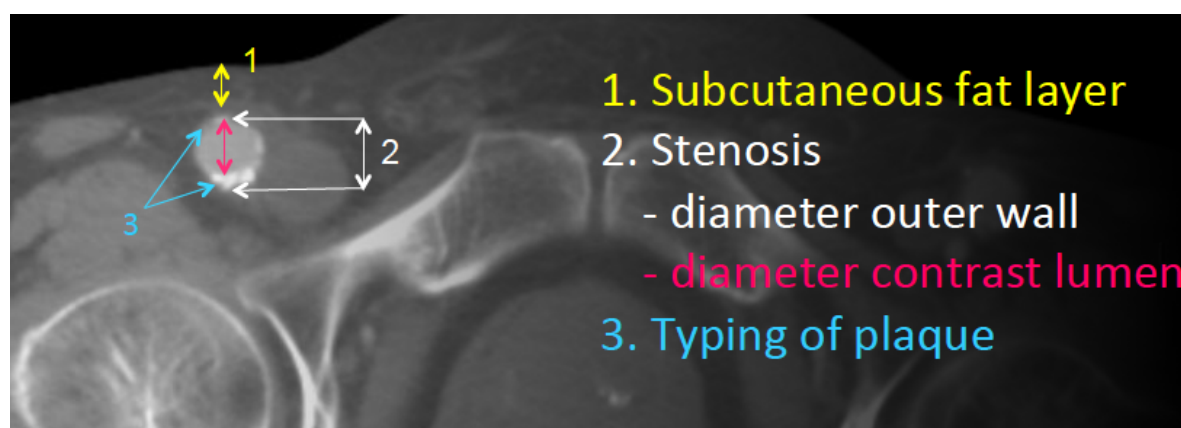


Figure 11. Stenosis calculation $(x\text{-diameter contrast lumen}/y\text{-diameter inner lumen}) \times 100$

3.3.3.2 Subcutaneous fat layer above in the groin

The subcutaneous fat layer was evaluated as a possible risk factor for failure of the technique as it previously had been described that obesity could be a contraindication to percutaneous EVAR approach.⁴ Instead of using body mass index (BMI) we used the subcutaneous fat layer lying above the stipulated puncture site as we thought this was a more logical measure to consider as it directly describes the presence of excessive fat in the area of interest instead of the whole body. The fat layer was measured in the anterior-posterior projection from the arterial wall to the skin (Figure 11).

3.3.3.3 Calcification of the femoral artery and grade of stenosis

Excessive atherosclerosis in the access vessels has previously been described as a risk factor for percutaneous EVAR with a possibly higher failure rate of percutaneous femoral closure.^{4,199} In order to evaluate this the plaque burden of the common femoral artery was

assessed at the assumed puncture site. After evaluating a number of access sites a grading system for describing the femoral calcification was agreed upon (*Figure 12*), which was used throughout the study. *Table 3* presents the definition of calcification grades used.



Figure 12. Grading system for assessing the calcification burden

Table 3 *Definition of calcification grades*

Plaque CTA	Definition
Grade I	No visible plaque
Grade II	<25 %
Grade III	>25 %
Grade IV	>50 %
Grade V	Anterior plaque

To evaluate the grade of stenosis the ratio was calculated between diameters of the mean inner contrasted lumen (x) and the mean outer vessel wall (y) of the common femoral artery at the assumed puncture site. A percentage-estimated stenosis was obtained through $(x/y \times 100)$. See *Figure 11*. At 1-year follow-up, comparing the preoperative with the postoperative assessed the change in grade of stenosis.

3.3.4 Closure of femoral access sites, the Fascia Suture Technique

In this study the fascia suture technique was evaluated. It was previously described by Dietrich 1997 and Larzon 2006.^{195,198}

Operative technique FST:

After completion of the EVAR procedure the introducer with its inner sheath is reinserted into the femoral artery and an approximately 4 cm long transverse skin incision is made. The subcutaneous layer is then bluntly dissected to the cribriform fascia overlaying the femoral sheath and lymphatic tissue of the groin. An inversed U-stitch in the cribriform fascia is placed using a non-absorbable monofilament 2-0 or larger suture. The stitch should include the access passage of the reinserted introducer and the area directly above the puncture site. After tightening the first throw of a conventional knot the introducer is withdrawn leaving the guide wire in place when accessing the hemostasis. If the hemostasis is considered sufficient the guide wire is withdrawn and the knot is further tightened and completed. If the first fascia

suture fails a second can be placed. If hemostasis is inadequate after a second fascia suture, a cut down should be performed.

The influence of introducer size (Fr) to the failure rate of the method was evaluated. The impact of FemoStop[®] use on outcome of FST was also studied.

3.3.5 Outcome measures

To evaluate the method, outcome measures were; primary success defined as adequate hemostasis and complications at 1-month and 1-year follow-up. Immediate failures were considered as:

- insufficient hemostasis resulting in a formal cut down and exposure of the artery and lateral arteriography with or without patch
- limb ischemia observed directly postoperatively, also resulting in formal cut down with arterial repair.
- other technical failures possibly resulting from the FST

At 1-month and 1-year follow-up the following were evaluated:

- any adverse event that could be linked to the FST including late postoperative bleeding, groin infection etc.
- presence of pseudoaneurysm at 1-month and 1-year CTA follow-up
- grade of stenosis observed at 1-year postoperative CTA related to preoperative measure at CTA (on 1-month follow-up CTA grade of stenosis was not calculated)

3.4 PATIENTS AND METHODS PAPER II

In Study II the aim was to analyze perioperative bleeding related to outcome in patients treated with EVAR for non-ruptured AAA and rAAA. The study population comprised 525 EVAR patients from two vascular centers. Data concerning the operative procedure i.e. stent graft devices, introducer sizes, and methods of closure of access sites were analyzed in order to find risk factors for increased perioperative blood loss.

3.4.1 Inclusion and data collection

This was a retrospective study of all patients treated with EVAR for non-ruptured and ruptured AAA at Malmö Vascular Center and the Department of Vascular Surgery at Karolinska University Hospital between 1st of April 2008 until 31th of August 2011.

Patients and comorbidities were identified from Swedvasc and entered into a database. Data was also retrieved from the local medical records and operative charts and added to the database concerning preoperative, operative and postoperative variables. Blood chemistry data was collected from the local laboratory databanks. Time of procedure was collected from the local computerized operative planning tool. The blood loss was retrieved from the Swedvasc and the anesthesiologists' operative charts.

The study cohort included 435 non-ruptured (elective n=382, symptomatic n=53) and 90 rAAA patients.

3.4.2 Data analysis and outcome measures

Subgroup analysis was performed as appropriate for the rAAA and non-rAAA (elective or symptomatic) groups in order to avoid case bias. The three groups constituted different categories of patients with regard to pathophysiology, hemodynamic status and difficulty in repair. Outcome measures were not deemed as comparable between the groups.

3.4.2.1 Perioperative blood loss

Perioperative bleeding was categorized into four groups according to Swedvasc based upon the estimated volume of blood loss: <1000 ml, 1000-1999 ml, 2000-5000 ml, and >5000 ml. The blood volume was crosschecked with the estimated blood loss in the anesthesiologists' operative chart. The perioperative blood loss was then correlated to preoperative and perioperative variables.

3.4.2.2 Femoral access site closure

The primary methods of closure for the femoral access sites were analyzed with regard to technical success and were related to perioperative blood loss.

3.4.2.3 Outcome measures

Thirty-day mortality was the primary outcome measure. Morbidity outcome measures studies were renal failure, multi organ failure (MOF), bowel ischemia, abdominal compartment

syndrome (ACS) and >5-days ICU stay. The outcome measures were analyzed in uni- and multivariable logistic regression models in relation to perioperative blood loss and other perioperative variables.

3.5 PATIENTS AND METHODS PAPER III

In Study III the aim was to analyze a number of preoperative coagulation parameters (known to be relevant to assess coagulopathy) and their association with preoperative hemodynamic status, perioperative bleeding, and outcome in patients presenting with rAAA. A retrospective single center study of rAAA patients undergoing either open (OR) or endovascular (EVAR) repair was conducted.

3.5.1 Inclusion and data collection

The Study cohort included 91 rAAA patients that presented to Karolinska University Hospital between 1st of May 2008 until 31st of August 2013. During the study period 121 patients with rAAA presented to our clinic. Thirty patients were excluded from the study due to missing data. The 30 excluded patients did not differ from the study cohort regarding demographics or outcome. The included patients were treated by open repair (OR) (n=72, 79%) or EVAR (n=19, 11%).

3.5.2 Laboratory data

Laboratory data were collected at the patients' arrival to the emergency department. Quality assured methods for analyzing blood samples were used. The blood samples analyzed are presented in Table 4.

Table 4. *Reference ranges of laboratory values used in Paper III*

Blood test	Reference range
Fibrinogen	[2.0-4.0 g/L; 200-400 mg/dL]
Hemoglobin	[female/male 117-153/134-170 g/L]
Platelet count	[165-387/145-348 10 ⁹ /L]
Prothrombin time ratio (PTR-INR)	[<1.2]
Activated partial prothrombin time (APTT)	[28-40 s]
S-Creatinine	[<90/<100 µmol/L]

3.5.3 Measuring perioperative bleeding

The blood loss was retrieved from Swedvasc and the anesthetists' operative charts. Perioperative bleeding was categorized into three groups according to Swedvasc based upon the estimated volume of blood loss: 0-1999 ml, 2000-5000 ml, and >5000 ml. The original categorization of four separate groups were adjusted into three groups by adding the <1000 ml and 1000-1999 ml groups together. There were two logical reasons for this. Firstly, in Paper II perioperative bleeding >2000 ml demonstrated a significant difference on outcome. Secondly, to avoid small groups making statistical analysis difficult.

The perioperative blood loss was correlated to pre- and perioperative variables.

3.6 PATIENTS AND METHODS PAPER IV

In this study the aim was to investigate the effect of blood transfusion and blood product ratios on outcome in massively transfused rAAA patients undergoing open repair or EVAR. The effects of early administration of FFP and PLT on outcome were analyzed as well as different transfusion strategies during the study period.

Patients were analyzed in total and separately as appropriate according to operative methods. Only patients that were massively transfused (MT) were analyzed with regard to transfusion ratios and time and association to outcome.

3.6.1 Inclusion and data collection

The study was performed at three of the largest vascular centers in Sweden; Karolinska University Hospital, Södersjukhuset (Stockholm) and Skåne University Hospital (Malmö). All rAAA patients in Swedvasc undergoing repair by EVAR or open surgery during the study period (May 8, 2008 to December 31, 2013) were considered for inclusion. The final study cohort consisted of 369 patients.

Massive transfusion (MT) was defined as ≥ 4 units RBC transfused in 1 h or 10 units of RBC transfused in 24 h.¹⁵⁷ Patients reaching either of the two definitions were declared as patients requiring MT.

Patients that died before aortic repair was attempted as well as patients that died in the operating theatre were excluded from analysis of transfusion ratios and timing as the transfusion strategy was considered not to determine their outcome.

Patient data, medical history and data related to the rAAA repair and outcome were collected from Swedvasc and the hospitals medical records. Blood transfusion data was captured from the local transfusion registries. The transfusion registries included data on exact issuing time, number of units and type of blood products ordered.

3.6.2 Method of repair

EVAR was the preferred primary method of repair in rAAA at the enrolled centers. However the vascular surgeon in charge decided upon the method of repair according to his or her judgment. The complexity of anatomy, hemodynamic status, personal competence in performing advanced EVAR or complex open repair, and the hospitals resources were all factors that were processed before deciding upon the method of repair.

3.6.3 Transfusion data and blood products

Red blood cells (RBC) were administered in units of 280 ml. The plasma units of approximately 250 ml were prepared as either fresh frozen plasma (FFP), stored in -30°C or fresh plasma stored up to 14 days at $+2$ – $+6^{\circ}\text{C}$. Platelets were prepared by centrifugation from four to six donors and kept at $+22^{\circ}\text{C}$ under continuous gentle agitation. Each unit contained

>240 x10⁹ platelets suspended in 350 ml, 70% platelet additive solution (PAS) and 30% plasma. All blood components were prestorage leukocyte reduced.

The recommended ratio of FFP:RBC transfusion in massively transfused patients in Sweden is, according to national guidelines, 1:1.¹⁵⁹ The recommended ratio of PLT:RBC is defined to 1:4 and not 1:1, as in Sweden a transfusion unit of PLT are pooled from 4-6 donors.

3.6.4 Outcome measures

The primary outcome measure was 30-day mortality.

The variable “Any complication” in Swedvasc was chosen for morbidity. The methodology used when measuring associations is presented in the statistical considerations section for Paper IV.

3.7 STATISTICS

3.7.1 General statistical considerations Papers I-IV

Descriptive statistics, including means, medians, standard deviations, ranges, interquartile ranges (IQRs) and proportions, were calculated as appropriate.

Chi-square, Mann-Whitney U tests, Kruskal-Wallis Test, Students T test or Fisher's exact tests were used, to compare nominal variables between data as appropriate. Chi-square tests were performed for contingency tables. The Wilcoxon signed rank test was used for paired data. Significant relationships in univariable and multivariable logistic regression models were expressed as odds ratio (OR) with 95% confidence interval (CI). P-values of <0.05 were considered as statistically significant.

3.7.2 Statistics Paper I

As distribution of data was skewed, nonparametric tests were performed. In addition to the analysis of the suggested predictors of FST failure (i.e. preoperative CFA stenosis, plaque grade, and obesity), the size of the introducer sheath was evaluated. The introducer sheath diameters, range (14 to 24 F), were dichotomized as large (18–24 F) and small (14–16 F). Any influence of the FemoStop[®] on outcomes was also evaluated.

3.7.3 Statistics Paper II-III

Univariable analysis of binary, nominal and ordinate variables was performed. Variables associated with increased blood loss ($P<0.05$ in univariable analysis) were analyzed in a logistical regression model.

3.7.4 Statistics Paper IV

The associations between both a) time to first transfusion and thirty-day mortality and b) 24-hour ratio and thirty-day mortality were modeled using logistic regression. Associations for FFP and PLT were analyzed separately. Time to first transfusion was modeled as an interaction between a dummy variable indicating whether transfusion was received or not and a continuous variable measured in log (hours from first order of blood products+1). A main term for the dummy variable, but not the continuous variable, was included in the model. Both crude and adjusted analyses were performed. Time to first transfusion was adjusted for age. 24-hour ratio was adjusted for age and total amount of transfusion. The analyses were stratified according to operation type (endovascular or open repair).

As variable for morbidity the Swedvasc variable of “*Any 30-day complication*” was analyzed against transfusion volumes, timing and ratios. Cubic splines with three knots were used to relax the assumption of linearity between exposure and outcome whenever feasible.

To test if the 24-hour ratio of FFP to RBC and PLT to RBC changed during the study period, we compared the ratio for the years 2008 to 2010 with the ratio for the years 2011 to 2013 using a median test.

4 RESULTS AND DISCUSSION

In the following section the results for each of the papers are presented, followed by comments and discussions of the findings.

4.1 RESULTS AND DISCUSSION PAPER I

In Paper I the immediate success and failure rate of the fascia suture technique for closing the femoral access site after EVAR was analyzed. A total of 160 femoral access sites out of 100 consecutive EVAR patients were studied.

4.1.1 Short and mid-term results

The technical success was 146/160 (91%). The 14 failures were converted to open exposure of the femoral artery and raphie intraoperatively or in direct conjunction to the primary surgery. Eleven were due to inadequate hemostasis and 2 due to limb ischemia following the femoral access site closure. One patient had to be opened because of a broken guide wire tip that had to be retrieved.

At 30-day follow-up 2 complications were detected. The first complication was a late postoperative bleeding 2 weeks after the procedure that presented to the emergency ward. The second was an infected pseudoaneurysm that also presented after 2 weeks. Both cases had to undergo emergency surgery and the infected pseudoaneurysm was also treated with intravenous antibiotics. No other complications were noted at 1-month follow-up.

At the 1-year follow-up nine <1 cm pseudoaneurysms were suspected on CTA. None of these required extra follow-up or treatment. Data presented in *Table 5*.

Table 5. *Outcome Fascia Suture Technique*

<i>Immediate outcome & follow-up of femoral closures by Fascia Suture Technique</i>		
Immediate Outcome (n=160)	1-month (n=146)	1-year (n=146)
146 (91%) technically successful	144 successful	137 successful
14 failures: 11 bleeding 2 limb ischemia 1 broken guide wire	2 complications: 1 bleeding 1 infected PA	9 complications: 9 <1 cm PA (Conservative treatment)

PA = pseudoaneurysm

4.1.2 Risk factors for failure of Fascia Suture Technique

The possible influence of the diameter of the introducer sheaths to the outcome of the FST was evaluated. There was no correlation between failure and introducer size ($p=0.803$). The use of FemoStop[®] (used in 55% of cases) had no influence on the FST outcome ($p=0.866$).

No preoperative risk factors predicting failure of FST were found. Patients with a deeper subcutaneous fat layer were not significantly more prone to a higher failure rate of FST ($p=0.08$). The calcification at the femoral access sites did not influence outcome of the FST ($p=0.12$). Distribution and outcome between Grade I-V presented in *Table 6*.

Table 6 *Distribution of calcification grades in cohort and immediate failures*

<i>Calcification as a Possible Risk Factor for FST failure (n=145)</i>		
	Primary hemostasis	Failure
Grade I (n=50)	47	3
Grade II (n=32)	31	1
Grade III (n=26)	22	4
Grade IV (n=11)	11	0
Grade V (n=27)	22	5
Total (n=145)	132	13

The grade of stenosis was not significantly related to worse outcome of the technique ($p=0.23$).

4.1.3 Discussion Paper I

4.1.3.1 General comments

Study I evaluated the short and mid-term results of the FST for closure of femoral access sites after EVAR.

The technique seems to be safe and effective, and simple to use. Preoperative obesity, femoral calcification, stenosis or large diameter introducer sheaths did not affect the outcome in this study.

4.1.3.2 Short and mid-term results

The 91% success rate of the FST in this study was similar to that described in other studies.^{105,195,200} Compared to other methods of closing the femoral access sites after EVAR it offers similar safety and complication rates. Numerous trials evaluate the preclose method (double ProStarXL®) for closure of femoral access sites.^{108,201,202} According to a meta-analysis 2013 the overall success rate for the preclose technique was 94% per femoral access.¹⁰⁸

4.1.3.3 Pseudoaneurysms

The clinical significance of the pseudoaneurysms noted at 1-year follow-up is unknown. It is difficult to compare the frequency of pseudoaneurysms observed in this study to that of other closure methods as many studies have used duplex ultrasound or simply clinical examination

at follow-up. Other studies have also reported postoperative pseudoaneurysms after FST ranging from 3% - 13.9%.^{105,195,200} The reported intervention rate at 1 year was however <1%. It should be noted that the presence of these small pseudoaneurysms could pose a potential danger for late complications if they should grow in size. No late follow-up reports have yet been published.

A valid skepticism still exists towards the FST and few centers use this method as the first choice for closing the femoral access sites. However there are indications that the method is gaining popularity.²⁰³

4.1.3.4 Possible risk factors for FST failure

The study includes 14 early failures and two 1-month complications, representing a 9% failure/early complication rate. Statistical analysis for preoperative risk factors is bound to be questionable due to the small number. A larger material would better help us investigate risk factors and avoid a type B statistical error. As described by others, the FST seems to function well also in patients with deep groins or in patients with calcified arteries.²⁰⁴

A subjective caution to avoid heavy calcification on the anterior wall has been described.²⁰³ In this study anterior plaque in the area of the puncture site was not deemed as significantly associated with failure. When calculating significance of difference in failure rates between the Grade V plaques against the other plaque grades I-IV a p-value of 0.06 is found in a contingency test using Chi². It could be argued that the failure to reach a significant p-value is due to a type B error. A cautious approach towards using FST for deep femoral groins and femoral arteries with anterior plaque could be suggested.

The number of femoral access sites in this study did not demonstrate an increased risk of postoperative stenosis.

4.1.3.5 Limitations

The main limitations are the cohort size number and the retrospective nature. A prospective randomized trial comparing FST with other methods of closure would be preferable. In this study no comparable method of closure was studied and the comparison to other methods can only be done by comparing results from other studies that may differ in case selection.

4.2 RESULTS AND DISCUSSION PAPER II

This study analyzed perioperative bleeding related to outcome in patients treated with EVAR for non-ruptured and ruptured AAA.

4.2.1 Study cohort

The study included 525 EVAR patients (435 non-ruptured AAA and 90 rAAA) from two vascular centers. The including data concerning demographics, comorbidities and medical therapies are presented in *Table 7*.

Table 7 *Demographics, comorbidities and medical therapy*

Factor	Non-ruptured AAA (n=435)	Ruptured AAA (n=90)
Age	73 (50-89)	74 (58-89)
Male sex	370/435 (85 %)	73/90 (81%)
<i>Comorbidities</i>		
Diabetes	31/286 (11 %)	13/60 (22 %)
Hypertension	210/283 (74 %)	41/55 (74 %)
Heart risk	105/278 (38 %)	24/55 (44 %)
<i>Blood Chemistry</i>		
Hb	135 (69-173)	131 (75-169)
s-Creatinine	93 (42-956)	109 (35-373)
PTr-INR	1.0 (0.8-4.6)	1.0 (0.9-3.1)
<i>Medical therapy</i>		
Acetylsalicylic acid	301/432 (69 %)	46/88 (51%)
Clopidogrel	15/431 (3.4 %)	None reported
Warfarin	42/432 (9.6 %)	5/88 (5.6%)

AAA- Abdominal Aortic Aneurysm; PTr-INR- Prothrombin time ratio-International Normalized Ratio

Data concerning the operative procedure and devices and methods of closure of access sites were analyzed in order to find risk factors associated with increased perioperative blood loss.

Out of the 435 non-ruptured AAA 53 patients were symptomatic AAA (10% of the total study cohort). Sixty-one patients got fenestrated EVAR and 18 were branched repairs. The median number of components used was 3 (range 1-6) and the median introducer size was 20 (range 11-24) for the ipsilateral side and 14 (range 11-14) for the contralateral side. In ruptured cases the median introducer size for the ipsilateral side was also 20 and the contralateral side was 16 (range 14-16). Median hospital length of stay was for non-rAAA patients 5 days (IQR=3) and for rAAA patients 9 days (IQR=11).

In patients that underwent percutaneous EVAR (n=422/525, 81%), fascia suture technique was the most common method of primary femoral access site closure (n=263/422, 62%) followed by double ProStarXL[®] suture mediated femoral closure (n=159/422, 38%). One hundred and one patients (101/525, 19%) underwent primary open femoral access.

Five out of the 525 patients were converted to open AAA surgery.

4.2.2 Perioperative bleeding related to preoperative and perioperative data

Table 8 shows the bleeding volumes in elective, symptomatic and ruptured AAA cases.

Table 8 Perioperative bleeding volume in non-ruptured and ruptured AAA

Volume (ml)	Elective n=382	Symptomatic n=53	Ruptured n=90	Total n=525
<1000	344 (90 %)	49 (93 %)	60 (67 %)	453(86 %)
1000 – 1999	29 (8 %)	2 (4 %)	11 (12 %)	42 (8 %)
2000 – 5000	8 (2 %)	1 (2 %)	10 (11%)	19 (4 %)
>5000	1 (<0.5 %)	1 (2 %)	9 (10 %)	11 (2%)

Table 9 Perioperative variables related to bleeding volume

Bleeding volume (ml)	< 1000 (n=453)	1000- 1999 (n=42)	2000- 5000 (n=19)	>5000 (n=11)	Total (n=525)	P value
<i>Method of Access and Femoral closure</i>						[523 (2 dead)]
Open access*	60	20	10	11	101	<0.001
Closure device*	156	2	1	0	159	
Fascia Suture*	235	20	8	0	263	
Ruptured	60	11	10	9	90	<0.001
Non ruptured	393	31	9	2	435	
Fenestrated (n) vs. standard	56	5	0	0	61	N/S
Branched (n) vs. standard	11	5	2	0	18	<0.001
Uni-iliac	13	0	4	1	18	<0.001
Introducer size **†	19	22	22	22	20	<0.001
Aneurysm diameter (mm) †	59	67	71	70	61	<0.001

*Primary Method of Access Site Closure (n= 523 patients) χ^2 according to Monte Carlo method,

**Ipsilateral side (median), †=Correlations according to Spearman. p-values refer to distribution differences across bleeding volume groups.

Co-morbidity, anti-thrombotic medication or analyzed preoperative laboratory chemistry data was not significantly associated with increased perioperative bleeding.

Open femoral access, fascia suture technique, branched or uni-iliac repair and aneurysm diameter were all associated with increased perioperative bleeding data presented in Table 9.

4.2.3 Outcome related to perioperative bleeding

The 30-day mortality for elective AAA treated by EVAR was 0.8%, for symptomatic 5.5% and for rAAA 21%.

4.2.3.1 Mortality related to perioperative bleeding

Multivariable logistic regression analysis found that perioperative bleeding >2 liters was significantly associated with increased mortality in non-rAAA OR 30; 95% CI [3.6, 145] $p=0.001$ and rAAA patients OR 10.68; CI 95% [3.2, 36.1] $p<0.001$. Data from calculations of total cohort is presented in *Table 10*.

Table 10 Univariable and multivariable analysis of factors influencing 30-day mortality total cohort

Effect	Univariable analysis			Multivariable analysis		
	OR	95 % CI	P value	OR	95 % CI	P value
Age > 80 y	2.8	1.2-6.6	0.02	-	-	N/S
Pre-op S-Creatinine > 120	3.3	1.4-7.3	0.004	-	-	N/S
Aneurysm diameter > 7 cm	4.8	2.0-11.8	0.001	-	-	N/S
Rupture	19.1	7.4-49.6	<0.001	10.6	3.8-29.6	<0.001
Bleeding > 2000 ml	30.8	12.2-77.4	<0.001	13.4	4.8-37.4	<0.001

Non-significant data is not presented. N/S-non-significant.

4.2.3.2 Morbidity related to perioperative bleeding

In non-rAAA and rAAA patients (data analyzed separately) postoperative morbidity (renal failure, MOF, >5 days ICU, bowel ischemia and ACS) was analyzed in a multivariable logistic regression model and was found to be significantly associated with perioperative bleeding >2 liters ($p<0.001$). *Tables 11* and *12* describe the complications in non-rAAA and rAAA patients.

Table 11 Outcome related to intraoperative bleeding in EVAR patients with non-ruptured Abdominal Aortic Aneurysms

Bleeding volume ml (Total 435)	< 1000 (393)	1000-1999 (31)	2000-5000 (9)	>5000 (2)	Total	P value
Dead 30-days (n)	4	0	2	0	6	<0.001
Renal failure (n)	7	0	1	2	10	<0.001
MOF (n)	0	0	1	2	3	<0.001
>5 days at ICU (n)	2	0	1	2	5	<0.001
Bowel ischemia (n)	1	0	0	1	2	<0.001
ACS (n)	1	0	0	2	3	<0.001

EVAR=Endovascular Aneurysm Repair, MOF = Multi Organ Failure, ICU = Intensive Care Unit, ACS = Abdominal Compartment Syndrome. χ^2 according to Monte Carlo method. P-values refer across groups.

Table 12 Outcome related to intraoperative bleeding in EVAR patients with ruptured Abdominal Aortic Aneurysm

Bleeding volume ml (Total 90)	< 1000 (60)	1000-1999 (11)	2000-5000 (10)	>5000 (9)	Total	P value
Dead 30-days (n)	6	2	5	6	19	<0.001
Renal failure (n)	3	1	2	3	9	<0.001
MOF (n)	4	1	1	4	10	<0.001
>5 days at ICU (n)	5	1	2	4	12	<0.001
Bowel ischemia (n)	3	0	2	2	7	<0.001
ACS (n)	2	0	2	3	7	<0.001

EVAR=Endovascular Aneurysm Repair, MOF = Multi Organ Failure, ICU = Intensive Care Unit, ACS = Abdominal Compartment Syndrome. χ^2 according to Monte Carlo method. P-values refer across groups.

4.2.4 Discussion Paper II

4.2.4.1 General comments

Paper II evaluated the perioperative bleeding in EVAR and the associated outcome for non-rAAA and rAAA. It is one of few previous studies that has evaluated outcome related to perioperative bleeding in acute and elective EVAR. Increased perioperative bleeding in open aortic surgery repair has been suggested as an independent risk factor for increased mortality and morbidity in previous studies but this has not been reported in EVAR before.^{1,2}

The findings suggest that measures should be taken to avoid large bleedings in order to reduce mortality and morbidity. The impact of antiplatelet medication on perioperative bleeding has not been evaluated. According to Paper II, 69% of non-ruptured AAA patients had ASA and 51% of the ruptured AAA.⁷⁷ Only a few were on double treatment with Clopidogrel. The use of ASA is similar or more prevalent in both elective and ruptured patients in this study compared to other reports.^{82,205}

It seems motivated to perform a risk analysis of each patient undergoing EVAR in terms of potential bleeding complications.

4.2.4.2 Outcome and perioperative bleeding

Paper II includes the contemporary EVAR outcome experience from two centers with both conventional and more advanced reconstructions.

4.2.4.2.1 Mortality and perioperative bleeding

The presented 30-day mortality rates for elective and ruptured cases are comparable to previous studies.^{112,185} This study shows that perioperative bleeding is not an insignificant problem in EVAR. A strong correlation between bleeding >2 liters and 30-day mortality in both non-rAAA and rAAA patients was found. The few elective patients with blood loss

exceeding two liters limits conclusions about the impact on mortality of large bleedings in this group.

The stronger correlation to mortality in multivariable analysis of perioperative bleeding >2 liters compared to rupture, could possibly be explained by patients with a contained rupture. Without on-going bleeding and need of massive transfusions, it seems that rAAA patients often recover fast after endovascular repair.

4.2.4.2.2 Morbidity and perioperative bleeding

Postoperative complications were also strongly correlated to perioperative bleedings >2 liters in non-rAAA and rAAA patients. Elective patients with blood loss exceeding two liters showed a significant correlation to postoperative complications.

4.2.4.3 *Perioperative bleeding and preoperative and perioperative data*

The study suggests that perioperative blood loss is not associated with comorbidities or preoperative laboratory blood chemistry and coagulation data. It seems most often to be related to technical issues, such as open femoral artery approach and access sites closure problems.

4.2.4.3.1 Preoperative bleeding and preoperative laboratory data

In this study no significant association between comorbidities, preoperative laboratory data and perioperative bleeding were found. The preoperative chemistry data including Hb, Creatinine and PTr-INR were analyzed. No other coagulation tests than PTr-INR were analyzed. PTr-INR has in previous studies been suggested to be associated with large bleedings and worse outcome in rAAA patients.²⁰⁶ Although previously argued as a preoperative marker for developing coagulopathy and hampered outcome PTr-INR seems in this study not to be predictive for increased perioperative bleeding.

4.2.4.3.2 Perioperative bleeding and access sites

Technical factors were important and it seems preferable to avoid open femoral artery access and to use small introducer sizes to decrease perioperative bleeding. Preparedness for large perioperative bleeding is necessary in ruptured AAA cases, but also in advanced EVAR cases, such as branched EVAR.

Open femoral access and closure by FST were associated with larger volumes of perioperative bleeding. It might be suggested that percutaneous EVAR should be advocated when possible in order to avoid unnecessary bleeding from the access sites. Patients undergoing FST bled more in this study. This is likely to be explained by the fact that more of the rAAA patients were found in this group. Direct percutaneous femoral puncture is usually preferred in rAAA patients with circulatory instability. FST for closure of the femoral arteries is then an attractive alternative as formal cut down and exposure of the arteries are avoided. No evaluation of the femoral plaque burden or subcutaneous fat layer was made in this study.

The safety of different methods of access site closure has previously been analysed.^{4-7,106} Excellent results for closure device (double ProStarXL[®]) used off label for larger introducers sizes than 18 Fr, and fascia suture have been reported with failure rates of 2-10 %.^{105,106} In this study, fascia suture and closure device were equally successful.

Large introducer sizes were also related to perioperative bleeding, which concurs with previous findings.^{5,107} Procedure time was not related to increased bleeding.

Branched EVAR were also risk factors for increased perioperative bleeding this could possibly be explained by the use of large introducer sizes in these procedures.

4.2.4.4 Limitations

This study is limited by its retrospective nature. It is likely that a prospective study would provide a better material for evaluation.

In patients undergoing EVAR for ruptured AAA, the internal blood volume loss is difficult to estimate. This is another limitation of this study. We based our estimation of the perioperative blood loss on established factors including blood-soaked lap sponges hemodynamic parameters and blood transfusion requirements. However, it is well known that, in surgical procedures in general, the perioperative estimated blood loss is both poorly reproducible and usually underestimated.¹⁵² In rAAA patients it may be possible to estimate the volume of the retroperitoneal or intra-abdominal hematoma using CT and 3D-volume rendering techniques, but this has not been established in AAA studies.²⁰⁷ The 3D-volume rendering techniques has previously been used in calculating volume of cerebral hematomas as a predictor for outcome.²⁰⁸

4.3 RESULTS AND DISCUSSION PAPER III

This study analyzed preoperative coagulation data in relation to perioperative bleeding, hemodynamic status and outcome in patients undergoing repair for rAAA.

4.3.1 Study cohort

During the study period, 568 patients underwent treatment for AAA at our center including 121 (21 %) patients with rAAA. Thirty rAAA patients were excluded from the analysis because of incomplete data. These patients did not differ from the study cohort in regards to demographics or outcome.

The study cohort included 91 consecutive patients with rAAA (median age 74 years [range: 57-91]; 80 % men) and complete preoperative laboratory data.

Demographics, comorbidities and risk factors are presented in *Table 13*. There were no patients on warfarin or low molecular weight heparin.

Table 13 *Patient demographics and procedure related data*

	<i>N=91</i>
Age (years)	74 y (57-91)
Male	73 (80 %)
<i>Comorbidities & risk factors</i>	
COPD	18/85 (22 %)
Diabetes	12/88 (14 %)
Hypertension	59/85 (69 %)
Heart disease	30/81 (37 %)
Previous stroke	9/84 (11 %)
Smoker*	31/53 (58 %)
Aneurysm diameter	75 mm (IQR 29)
EVAR	19 (21 %)
Open repair	72 (79 %)
Lowest preoperative BP (median)	60 mmHg (IQR 40)
<i>Intraoperative bleeding</i>	
<1999 ml	35 (39 %)
2000-4999 ml	33 (36 %)
>5000 ml	23 (25 %)

*COPD=Chronic Obstructive Pulmonary Disease. *=On going or abstain <5 years ago. Percentages in brackets refer to distribution within each comorbidity/risk factor.*

Open surgical repair was performed in 72 patients (79 %) including straight tube grafts (n=46), aorto bi-iliac (n=22) and aortobifemoral (n=4). There were 19 (21 %) patients that underwent EVAR.

None of the EVARs were performed with fenestrated grafts. Resuscitative percutaneous balloon occlusion of the aorta (REBOA) was used in 5 EVAR and 5 open surgical cases. One patient with rAAA was previously treated with EVAR.

4.3.2 Preoperative laboratory data

Preoperative laboratory data in patients arriving in the emergency department with rAAA are presented in *Table 14*. There was no significant difference in laboratory data related to gender or comorbidities.

Table 14 Preoperative laboratory data in patients (n=91) arriving in the emergency department with ruptured abdominal aortic aneurysm

Test	Median (IQR)	Normal value
Hemoglobin g/L	115 (IQR 36)	117-170 g/L
APTT (s)	40 (IQR 19)	28-40 s
Platelet count ($10^9/L$)	167 (IQR 104)	165-348 $10^9/L$
P-Creatinine ($\mu\text{mol/L}$)	112 (IQR 48)	<90 / <100 $\mu\text{mol/L}$
PTr-INR	1.2 (IQR 0.5)	<1,2
Fibrinogen (g/L)	1,8 (IQR 1,4)	2,0-4,0 g/L

IQR- interquartile range

4.3.3 Preoperative coagulation data and blood pressure

Preoperative fibrinogen and platelet concentrations showed linear relationships with preoperative blood pressure (BP) ($r=0.477$, $p=0.01$) and ($r=0.247$, $p=0.05$) respectively (*Figures 13 and 14*). The platelet correlation was not as strong as that of fibrinogen and BP.

Figure 13

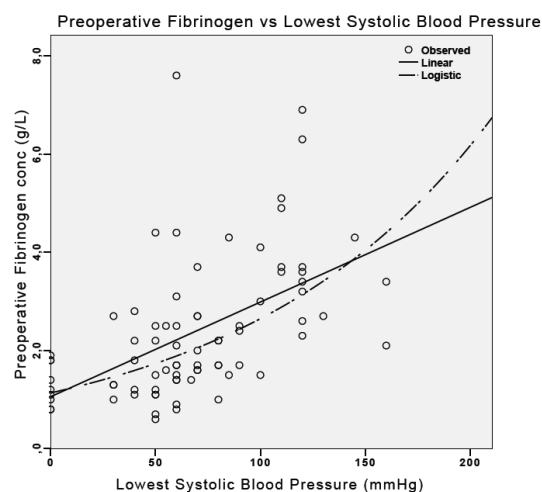
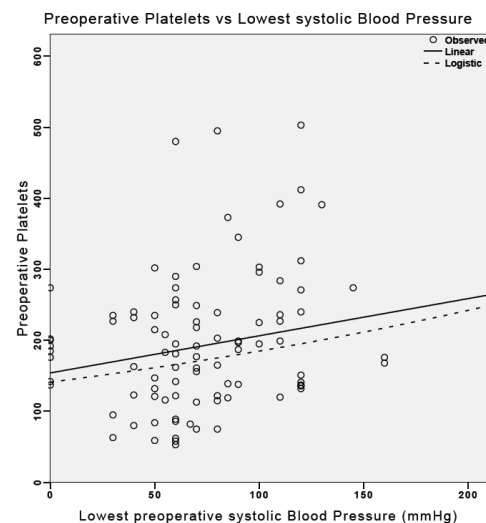


Figure 14



Patients with a blood pressure <70 mmHg had a median fibrinogen concentration of 1.4 g/L (IQR 1.0) compared to patients with blood pressures ≥70 mmHg who had a median fibrinogen concentration of 2.5 g/L (IQR 1.9) (P= 0.001)(Figure 15).

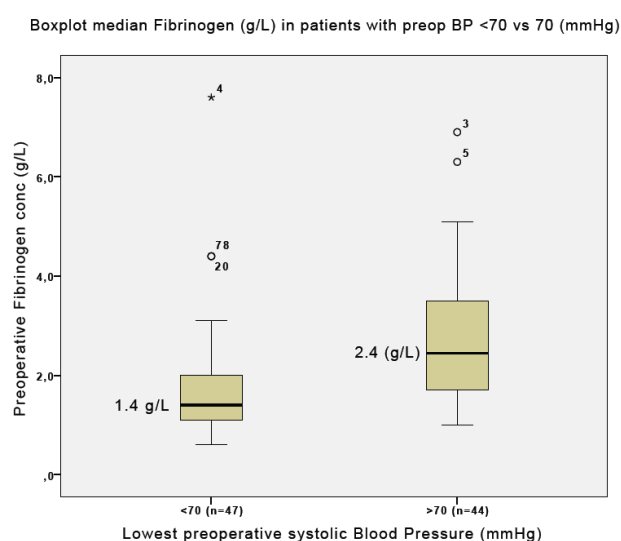


Figure 15. Box plot of preoperative fibrinogen and blood pressure

4.3.4 Preoperative coagulation data and perioperative bleeding

Preoperative fibrinogen concentration and platelet count were associated with perioperative bleeding. Lower preoperative fibrinogen concentrations and platelet counts were significantly associated with larger perioperative bleeding volumes. (P <0.001 and P = 0.024 respectively), data showed in Table 15.

Table 15 Preoperative laboratory tests in relation to volume of intraoperative bleeding

Bleeding volume ml (n)	< 1999 ml (n=29)	2000-4999 m (n=26)	>5000 ml (n=19)	P-value
Hemoglobin [g/L]	115 (IQR 37)	114 (IQR 32)	116 (IQR 39)	n/s
S-Creatinine (μmol/L)	106 (IQR 43)	113 (IQR 42)	120 (IQR 65)	n/s
PTtr-INR	1,2 (IQR 0,2)	1,3 (IQR 0,7)	1,2 (IQR 0,4)	n/s
APTT (s)	37 (IQR 16)	44 (IQR 18)	42 (IQR 21)	n/s
Platelet count [10 ⁹ /L]	178 (IQR 95)	167 (IQR 118)	132 (IQR 99)	0,024
Fibrinogen median g/L	2.3 (IQR 1.4)	1.6 (IQR 1.5)	1.4 (IQR 1.0)	<0,001

Median values (IQR=interquartile range), P-values across groups using Independent-Samples-Kruskal-Wallis Test

In the multivariable logistic regression analysis (adjusting for the following statistically significant variables in the univariate analysis: age >80 years, Creatinine >120 μmol/L, blood pressure <70 mmHg, fibrinogen <1.5 g/L, and previous stroke), fibrinogen <1.5 g/L

OR 10.04; 95% CI [1.8, 57.1], ($P = 0.009$) and blood pressure <70 mmHg OR 3.7; 95% CI [1.1, 12.5], ($P = 0.034$) were associated with IOB >2000 ml.

A preoperative blood pressure below 70 mmHg was also associated with large IOB >5000 ml OR 5.2; 95% CI [1.3, 21.1], ($P = 0.021$).

4.3.5 Preoperative coagulation data and outcome

The total 30-day mortality was 33 % (30/91; open repair 37.5% 27/72; 15.8% EVAR 3/19). *Table 16* shows the difference in preoperative variables for the two repair techniques. Other preoperative laboratory variables were not significantly different between the repair techniques.

Table 16 *Preoperative variables and method of repair*

	Open repair	EVAR	p value
Fibrinogen median (g/L)	1.7 (IQR 1.3)	2.3 (IQR 1.3)	$p = 0.014$
Platelets median ($10^9/L$)	162 (IQR 107)	183 (IQR 132)	$p = 0.011$
Preoperative blood pressure (mean) (mmHg)	61 (SD 34)	91 (SD 39)	$p = 0.001$

Postoperative complications among 30-day survivors included MOF (22%), ACS (17%), relaparotomy for bleeding (11%), bowel ischemia (13%), MI and stroke (2% respectively).

Low fibrinogen concentration (<1.5 g/L), elevated s-Creatinine (>120 $\mu\text{mol/L}$), low blood pressure (<70 mmHg), previous stroke, and perioperative bleeding >5000 ml were all associated with 30-day mortality in the univariate analysis. In the multivariable logistic regression analysis only previous cerebrovascular events OR 15.91; 95% CI [2.2, 115.07], ($p = 0.006$) and IOB >5000 ml OR 4.89; 95% CI [1.23, 19.46], ($p = 0.024$) were significantly associated with mortality (fibrinogen concentration <1.5 g/L OR 1.49; 95% CI [0.35, 6.29], ($p = 0.59$).

4.3.6 Discussion Paper III

4.3.6.1 General comments

In Paper III the association between preoperative coagulation tests, hemodynamic status, perioperative bleeding and outcome were analyzed in patients undergoing repair for rAAA. Low preoperative fibrinogen and platelet concentrations were significantly associated with preoperative hypotension and increased IOB in patients with rAAA. Extensive hemorrhage in rAAA is associated with high mortality and immediate measures should be taken to limit the blood loss and correct coagulopathy.

By finding early predictors for critical bleeding direct proactive measures could be taken.

The development of coagulopathy in patients with rAAA has been described in previous studies¹⁷⁰⁻¹⁷². It is one of the strongest predictors of poor outcome and it is vital to detect it early.^{170,209}

The role of fibrinogen has gained increasing focus in the risk analysis of perioperative bleedings and coagulopathy in trauma, orthopedics and in the cardiovascular literature.^{210,211} Fibrinogen has been suggested for early proactive use in severely bleeding aortic aneurysm patients, as well as in trauma and cardiac bypass patients.²¹²⁻²¹⁵

The overall mortality and morbidity outcome was comparable to that of other studies. EVAR was associated with a better outcome. However, selection bias in method of repair was suspected since preoperative blood pressure, fibrinogen and platelet concentration differed significantly between the OR repaired patients and EVAR patients.

4.3.6.2 Fibrinogen and rAAA

Fibrinogen acts as one of the key factors in the coagulation cascade by being transformed into fibrin through the help of thrombin. Its' function and contribution in hemostasis is more precisely described in the Introduction, *Section 1.4.2.2*.

According to literature review only one previous study has analyzed preoperative fibrinogen in rAAA patients.¹⁷³ In Study III, it was observed that patients presenting with hemodynamic shock with a blood pressure <70 mmHg, had an associated median fibrinogen concentration of less than 1.5 g/L. Fibrinogen deficiency in rAAA is believed to occur due to extensive blood loss and consumption of clotting factors. In addition, activation of the fibrinolytic system, acidosis, hypothermia, and metabolic changes also affect fibrinogen polymerization and metabolism.²¹⁶ It has been shown that rAAA activates anti-inflammatory processes.²¹⁷ It is possible that these processes affect fibrinogen concentration. During major hemorrhage there are indications that fibrinogen reaches a critical threshold earlier than other procoagulatory factors or platelets.

Preoperative fibrinogen values (<2 g/L) were observed in patients with >2000 ml perioperative bleeding. A fibrinogen concentration of less than 1.5 g/L was independently associated with intraoperative blood loss of more than 2000 ml in the logistic regression analysis. Preoperative fibrinogen <1.5 g/L was in univariable analysis significantly associated to increased mortality rate. In multivariable logistic regression no significant correlation was seen. The difference in preoperative values of fibrinogen and platelets between the two operative methods imply a difference in selection for the repair methods with more severely hypotensive patients in the OR group.

The Clauss method is the most common method of measuring fibrinogen concentration and was used in this study.²¹⁸ The test is based on the time for fibrin clot formation by adding an excess amount of thrombin to a centrifuged plasma sample and thereby activating the

fibrinogen into a fibrin clot. Emergency laboratories can normally present a result within 30 minutes.

Fibrinogen concentration and function can be estimated through viscoelastic tests (TEG and ROTEM). These tests are promoted as quicker (approximately 15 minutes) and assess many parts of the coagulation. They have in previous studies shown promising and interesting results in both trauma and elective vascular patients.^{219,220} The clinical value in patients with rAAA is yet to be evaluated.

4.3.6.3 Platelets and rAAA

Platelets are an essential part of hemostasis. Their function is described in more detail in Introduction, *Section 1.4.2.1*. In large bleeding they are consumed and their advanced functions can be hampered by a number of factors. It is of essence to have enough platelets in the blood volume in order for the blood still to be able to clot. The exact threshold for when to transfuse platelets varies. Standard laboratory platelet count estimates the platelet number or concentration in the blood. The method does not reflect the quality of platelet function.

Previous investigation about platelet consumption in rAAA patients has shown a significant correlation between low platelet count ($<150 \times 10^9/L$) on admission and mortality.²²¹ Suggested threshold values for platelet concentration ($125-400 \times 10^9/L$) are probably not correct for this patient category.

Decreased platelet counts were associated with increased perioperative bleeding. The preoperative platelet concentrations were however not below $100 \times 10^9/L$ even in patients that had perioperative bleeding volumes >5000 ml. Lower platelet concentration was also significantly associated with preoperative hypotension. It can be argued that the observed decrease in platelet concentration is of clinical insignificance. It could also represent a stronger resilience of the platelet concentration to hypotensive hemodynamic status in rAAA patients or that platelet concentration measurement is not specific enough to detect early deviations in platelet function and concentration.

Evaluation of point-of-care tests should be a natural path forward to gain deeper knowledge. In future these tests might be important in patients with rAAA.

4.3.6.4 Limitations

Paper III was a retrospective study and limitations apply. The cohort was contemporary and consecutive. The outcome analysis did not separate the operative methods (OR/EVAR). A larger cohort would make it possible to perform further subgroup analysis. A selection bias when choosing operative method is likely. It was difficult to evaluate the exact time for the preoperative laboratory tests in relation to the rupture and patient arrival in the emergency department. Blood samples in all patients were stated as preoperative in the medical records and laboratory database. A few patients might have started transfusions in close conjunction to the first laboratory tests. Preoperative fluid resuscitation was managed through permissive hypotension and crystalloids were only given in small boluses according to local protocol. The volumes of crystalloids given were difficult to evaluate.

4.4 RESULTS AND DISCUSSION PAPER IV

In Paper IV massive transfusion in patients with rAAA was analyzed.

4.4.1 Study cohort

During the study period a total of 406 patients underwent rAAA repair at the enrolled centers. Twenty-nine of these patients were excluded due to failure to match with the transfusion registry and 8 patients lacked transfusion data. A total of 369 rAAA patients undergoing repair was included. Demographics and comorbidities are presented in *Table 17*. 173 (47 %) EVAR and 196 (53 %) OR were performed with median RBC transfusion 8 u (IQR 4-14) and 14 u (IQR 8-28), respectively.

Table 17 *Demographics and comorbidities*

	Massive transfusion (n=261)	rAAA without massive transfusion (n=108)	Patients treated with EVAR (n=173)	Patients treated with open surgery (n=196)
Age	76 (70-82) ^a	78 (71-82) ^a	77 (72-83) ^a	76 (69-81) ^a
Male	212 (81%)	85 (79%)	136 (79%)	161 (82%)
Hypertension ^b	146 (78%)	51 (65%)	78 (70%)	119 (76%)
COPD ^c	48 (30%)	14 (20%)	27 (30%)	35 (26%)
Heart Risk ^d	83 (45%)	22 (30%)	45 (42%)	60 (39%)
Diabetes ^e	30 (15%)	17 (20%)	24 (20%)	23 (14%)
Previous stroke ^f	35 (21%)	10 (15%)	14 (17%)	31 (20%)
RBC transfusion	13 (8-23)	2 (2-4)	6 (3-11)	12 (7-23)

^a Median (25th percentile, 75th percentile), ^b Data missing for 28% of patients, ^c COPD=Chronic Obstructive Pulmonary Disease, Data missing for 38% of patients, ^d Data missing for 30% of patients, ^e Data missing for 22% of patients, ^f Data missing for 37% of patients, rAAA=ruptured Abdominal Aortic Aneurysm, EVAR=Endovascular Aortic Repair

4.4.2 Overall blood transfusions

In *Table 18*, the overall transfusion data in massively transfused patients (n=261; 71%) and patients that did not require massive transfusion (MT) (n=108; 29%) are presented. EVAR patients with MT (n=96) required significantly less blood transfusion compared to patients undergoing OR (n=165) (p<0.001, median test).

Table 18 *Transfusion data and FFP:RBC PLT:RBC ratios in MT and non-MT patients*

	Massively transfused EVAR (n=96)	Massively transfused open surgery (n=165)	Non-massively transfused EVAR (n=77)	Non-massively transfused open surgery (n=31)
RBC	10 (6-16.5)	15 (9-26)	3 (2-4)	2 (2-3)
Plasma	6 (2-14.5)	13 (7-24)	0 (0-1)	2 (0-5)
Platelets	0 (0-2)	2 (0-4)	0 (0-0)	0 (0-1)
FFP:RBC	0.59 (0.33-0.86)	0.84 (0.67-1.02)	0 (0-0.25)	0.67 (0.33-1.33)
Platelets:RBC	0 (0-0.17)	0.12 (0-0.18)	0 (0-0)	0 (0-0.22)

Values presented as median and inter quartile range (IQR=25th-75th percentile) RBC=Red Blood Cells, FFP=Fresh Frozen Plasma, PLT=Platelets

4.4.3 Ratios of FFP:RBC and PLT:RBC in massively transfused patients

The correlation between transfused FFP and RBC was significant $p < 0.001$ as demonstrated by *Figure 16*. For all patients the median blood product ratios were 0.67 (IQR: 0.28-1) for FFP:RBC and 0.03 (IQR: 0-0.16) for PLT:RBC. Median blood product ratios for FFP:RBC were: for EVAR 0.59 (IQR: 0.33-0.86) and OR 0.84 (IQR: 0.67-1.2); $p < 0.001$].

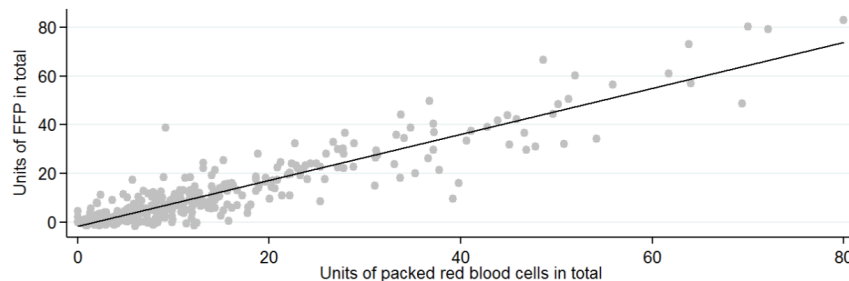


Figure 16 Relationship FFP:RBC in all rAAA patients. Plotted overall ratio of units of fresh frozen plasma against units of packed red blood cells, calculated after the first 24 hours from first order of any blood product.

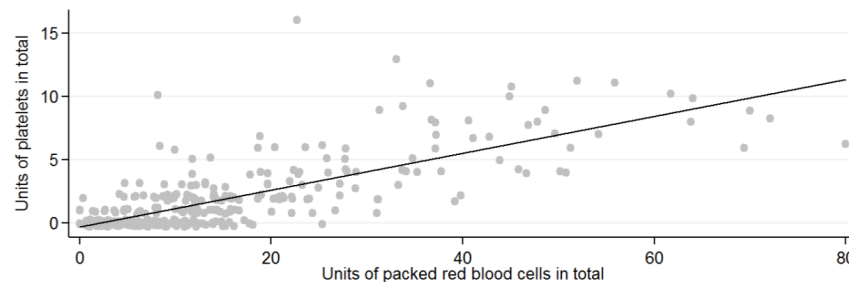


Figure 17. Relationship PLT:RBC in all rAAA patients. Plotted overall ratio of units of and units of platelets against units of packed red blood cells, calculated after the first 24 hours from first order of any blood product.

The transfused ratio of PLT:RBC in the whole group was 0.14 as demonstrated by *Figure 17*. The relationship between transfused PLT and RBC was significant $p = 0.024$.

There was a significant difference in ratios between patients repaired with EVAR and open surgery PLT:RBC ratio EVAR 0 (IQR: 0-0.17) and for the OR group 0.12 (IQR: 0-0.18); $p < 0.001$.

4.4.4 Time dependent ratios and timing of ordering blood products

For patients requiring MT the blood product ratios increased over the studied 24 h after the first transfusion order. *Figure 18* plots the changing ratios over time. Both FFP:RBC and PLT:RBC ratios showed to be very low in the early hours to consequently increase to a steady ratio after about 2.5 hours.

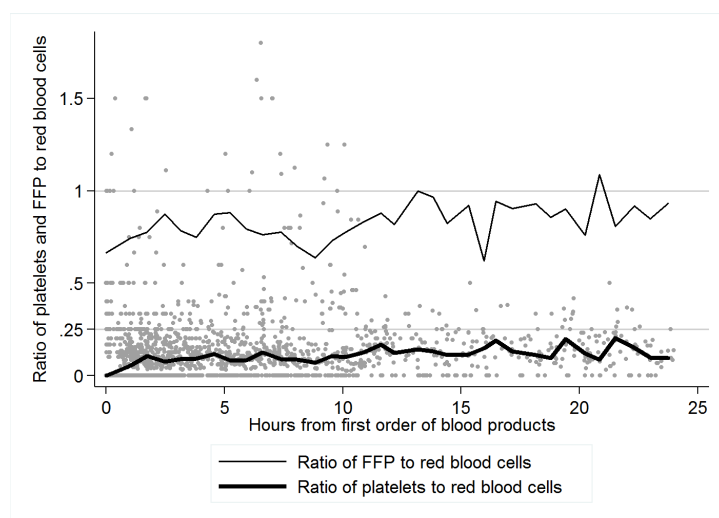


Figure 18. Relationship FFP:RBC and PLT:RBC in all rAAA patients. The curves represents the changes in ratios of [plasma/red blood cells] and [platelets/red blood cells] for massively transfused patients plotted against time (h) during the first 24 hours after the first orders of blood transfusion.

4.4.5 Ratios and time of first transfusion of FFP and PLT related to outcome

The FFP:RBC ratio was associated with 30-day mortality in patients undergoing open repair as shown in *Figure 19*. As the ratio approached 1 the risk for mortality was reduced ($p=0.003$, logistic regression adjusted for age and total amount of transfusion). The same relationship was not seen in patients undergoing EVAR.

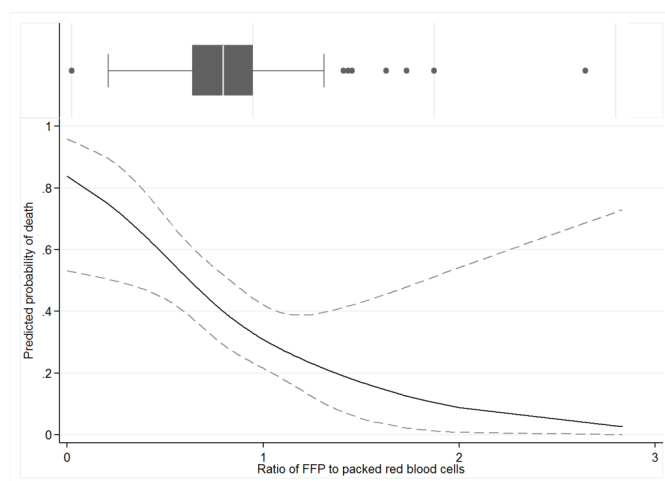


Figure 19. Predicted risk of mortality against ratio units of fresh frozen plasma to units of red blood cells for patients undergoing open repair. Horizontal boxplot plotted above curve to show distribution. Curve adjusted for the average values of age and total transfusion in the massively transfused open repair group.

No significant association between PLT:RBC ratio and 30-day mortality was seen.

Delayed PLT transfusion in patients undergoing open repair or EVAR was associated with 30-day mortality as shown in *Figures 20* and *21*. Transfusion of platelets (compared to no transfusion) was also significantly associated with increased risk for OR patients, odds ratio

2.93; 95% CI [1.04, 8.23] but not for EVAR patients, odds ratio 2.05; 95% CI [0.55-7.58]. A similar relationship could not be shown for time of first FFP and 30-day mortality as the vast majority of patients got plasma very early.

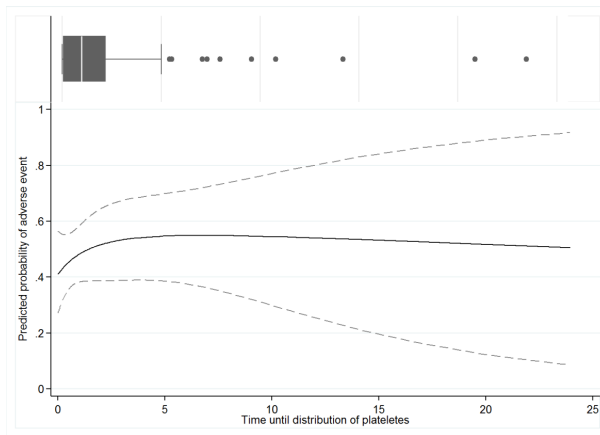


Figure 20. The predicted risk of mortality plotted as a curve against time (h) until transfusion of platelets in open repaired patients. Horizontal boxplot of distribution plotted above curve. Odds ratio calculated by logistic regression (adjusted for age) OR: $P=0.012$. Curves adjusted for the average values of age.

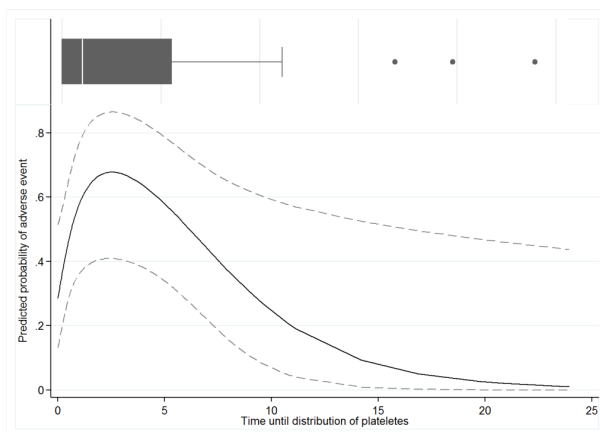


Figure 21. The predicted risk of mortality plotted as a curve against time (h) until transfusion of platelets in patients undergoing EVAR. Horizontal boxplot of distribution plotted above curve. Odds ratio calculated by logistic regression (adjusted for age) EVAR: $P=0.003$. Curves adjusted for the average values of age.

4.4.6 Hemodynamic status and blood transfusion

The lowest preoperative systolic blood pressure was inversely correlated to the number of total units RBC received as presented in Figure 22.

Patients presenting severely hypotensive received earlier transfusion of FFP and PLT than normotensive patients.

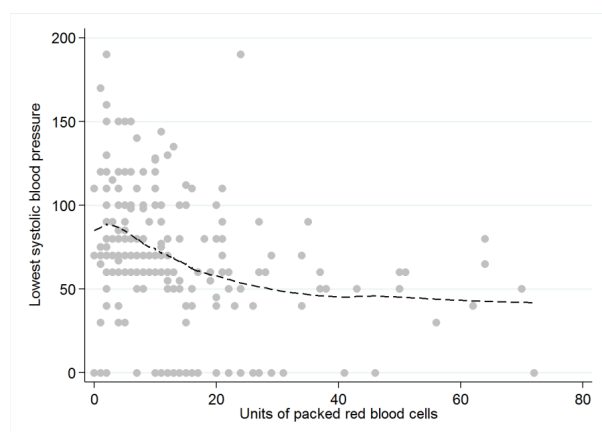


Figure 22. Lowest preoperative systolic blood pressure (mmHg) vs. total amount of units of packed red blood cells given.

4.4.7 Changes in transfusion ratios over the course of the study

Over the study-period, median PLT:RBC ratio increased significantly in massively transfused patients, as demonstrated in *Figure 23* ($p < 0.001$, median test). The median PLT:RBC ratio for 2008-2010 was 0.07 while the median PLT:RBC ratio for 2011-2013 was 0.14. The same trend was not seen for FFP:RBC ratio ($p = 0.10$, median test).

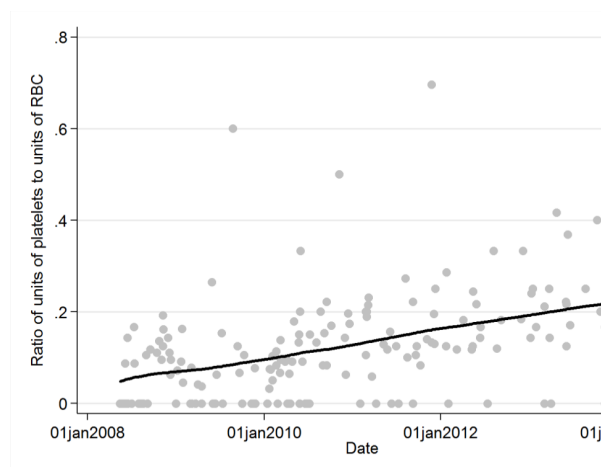


Figure 23. The 24 h ratios of units of platelets/units of packed red blood cells in massively transfused patients plotted against time (dates) during the study period.

4.4.8 Discussion Paper IV

4.4.8.1 General comments

In Paper IV the effect of blood transfusion and blood product ratios on outcomes in rAAA patients were analyzed. Seventy one percent of all patients undergoing rAAA repair required massive transfusion and more than half of the patients undergoing EVAR required massive blood transfusion. The overall transfusion requirements were lower in the EVAR group compared to open surgery. The ratios of FFP:RBC and PLT:RBC were significantly lower in the EVAR group. A FFP:RBC ratio close to one was associated with a lower risk for mortality. A significant survival advantage was suggested in patients receiving early PLT transfusion.

4.4.8.2 Transfusion in rAAA patients

A lower than expected PLT:RBC ratio in both open repaired and EVAR patients was found. Also a delay in the transfusion of PLT was observed. This diverges from the massive transfusion guidelines adopted at the enrolled centers. The massive transfusion protocols suggest transfusion in ratios 1:1:1 and early transfusion of platelets. Universal donor blood in packages of 4 U RBC and 4 U FFP are usually available at the emergency departments at the enrolled centers. In rAAA patients with hemodynamic impairment these emergency packs (at some centers referred to as “trauma packs”) are entered into the transfusion registries a posteriori. A previous study has controlled this retrospective method to be accurate both in timing and in amounts of units.²²²

A later platelet transfusion is likely to be attributed to both the fact that no emergency PLT units are available at the ED and the fact that the threshold for PLT transfusion of platelet count of $<50 \times 10^9/L$ seldom is reached preoperatively in rAAA patients.¹⁶⁹ Another possible reason for delaying platelet replacement in aortic repair may be the possible risk of perioperative thrombosis. Also coagulopathy may be more difficult to diagnose in EVAR patients, which might explain the lower than recommended ratios of both FFP and PLT in this group. Perioperative point of care tests, i.e. thromboelastography, may be helpful to diagnose coagulopathy and tailor the hemostatic resuscitation.

Our results that transfusion ratios of FFP:RBC that approach 1:1 lower risk of mortality, concurs with previous findings. PLT:RBC ratios were not significantly associated with mortality in this study. It was noted that a few patients with extremely high ratios of PLT:RBC had higher mortality, this observation is likely to be explained by the fact that these patients suffered from surgically uncontrollable bleedings (and that platelets given were insufficient for controlling the bleeding and reversing the coagulopathy).

It might be reasonable to argue that the transfusion recommendations should differ between patients treated with EVAR compared to open repair given the different nature of the two methods of repair. Even though EVAR patients received smaller volumes of transfusion with lower FFP:RBC and PLT:RBC ratios compared to open repaired patients, a majority (55 %) required massive transfusion. This finding justifies further studies on transfusion strategies and management of coagulopathy in rAAA patients undergoing EVAR.

PLT:RBC ratio increased over the study period. The same observation was not seen for FFP:RBC ratio. This might be explained by that more aggressive and early transfusion of platelets in patients requiring MT has gained focus in recent literature. A general shift of improvement in bedside monitoring of coagulopathy and hemodynamic status might also contribute to this observation.

4.4.8.3 Limitations

This study carries limitations due to its retrospective design and the registries used for data collection. The data analyzed is retrieved from large registries, which might skew data and

must be taken into consideration when interpreting the results. The transfusion registry has previously been validated and shows accuracy regarding transfusion time and volume.²²² A variation in transfusion regimes in between individual anesthesiologists is likely. However, we believe the generalizability of data is satisfying considering inclusion of three large hospitals.

In order to better provide recommendations for optimal transfusion ratios and timing of blood products in treatment for rAAA, especially endovascular repair, prospective randomized trials may be needed.

5 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The overall aim of this thesis was to investigate different aspects of perioperative bleeding in patients undergoing open or endovascular repair for AAA. The perioperative management of patients with massive bleeding has been refined through increased knowledge in hemostasis surveillance, new methods for coagulation testing and therapeutics as well as in the field of transfusion and critical care. Extensive knowledge has especially sprung from the trauma literature. In vascular surgery there is still a need and opportunity for further investigation.

The embarked endovascular treatment era of AAA offers a minimally invasive method associated with decreased perioperative blood loss compared to open repair. This fact is a welcome progress for the patients awaiting repair of their diagnosed or undiagnosed AAAs. It justifies one of the preface questions; -Should really more time be invested in scientific research about perioperative bleeding in AAA repair. Bleeding poses a potential life-threatening condition for the rAAA patient undergoing repair also by EVAR, and yes there is a need for further investigation in patients with critical bleeding. *Papers II, III and IV* supports these statements.

It is clear from the included studies that outcome after AAA repair cannot only be measured in mortality. In *Papers II and IV* increased perioperative bleeding was significantly associated with increased morbidity. Morbidity measures can be questioned from registry studies as registry users might refrain from report and hence skew data to a more attractive heritage of the individual surgical doings. Mortality cannot be hidden in registry data but complications and suffering can. However there are ways to tackle this by letting professional registry administrators enter the data and by automated data retrieval from medical records. In pursuing further knowledge about the impact of perioperative bleeding proper and robust methods of detecting postoperative complications must be applied. A form of self-reporting through web-based surveys is probably one possible path to explore.

EVAR is a “tool intense” treatment option with high costs for the materials used. In the introduction it was described that previous literature supports the percutaneous access approach to EVAR instead of surgical cut down to the femoral arteries as it offers less complications and a faster procedure. *Paper I* studies and suggests the safe use of the fascia suture technique (FST). It can be used as an alternative to pricy closure devices for hemostasis in the femoral access sites. Other studies also supports the FST as safe but still its use is not routine practice at many centers.²⁰³ A considerable amount of money would saved in material costs on a yearly basis if all femoral access sites after EVAR would be closed by FST instead of all closed by ProStarXL®. A prospective randomized trial has recently been published, but additional investigations will be needed in order to verify that the results are reproducible.²⁰⁴

It is difficult to estimate the volume of bleeding correctly. Much of the bleeding volume data used in this thesis project relies on registry data. In the Swedvasc registry the estimated volumes are categorized by predetermined groups of bleeding volume. A better way would be if the estimated volumes reported into the registry were entered as a summed numeral in milliliters. In *Paper II* one of the aims was to find a cut off value for when bleeding starts to be critical. A volume of above 2000 ml seems to be related to increased risk for complications. Estimation methods for measuring blood loss need further evaluation. In the case of rAAA undergoing EVAR the preoperative bleeding cannot be evaluated through visualization and measurement through suction and surgical gauzes. An evaluation of the preoperative volume by computer tomography 3D volume rendering could be an alternative for estimation to explore.

Preoperative predictors for increased perioperative bleeding were studied in *Paper III*. Fibrinogen and platelet count were affected early by hemodynamic instability and more attention should be paid to these laboratory tests than previously have been described. The preoperative value (PTr-INR >1.2) was not significantly associated to perioperative bleeding in this cohort. Others have suggested this to be a marker for coagulopathy. Trauma patients arriving with a PTr-INR >1.2 had significantly higher mortality and transfusion requirements than patients with a normal PTr-INR.¹⁴⁶ Also severe APTT prolongations >1.8 times normal have been associated with bleeding but seems to be less sensitive than PTr-INR.^{223,224} Fibrinogen concentrations might add important value as a preoperative test, also in non-ruptured AAA, as it was found to be more sensitive than the other coagulation tests. This concurs with findings in previous studies analyzing blood loss and fibrinogen.^{210,225,226} Additional studies are needed in vascular surgery and AAA repair in particular.

Paper III suggests that rAAA patients with severe hypotension potentially could benefit from early administration of fibrinogen concentrates. This hypothesis certainly needs to be evaluated in prospective randomized clinical trials. Hemostatic therapy with fibrinogen concentrate in patients undergoing elective major aortic surgery at a single-center has significantly reduced the transfusion of blood products.²²⁷ In guidelines for management of bleeding following major trauma, treatment with fibrinogen concentrate is recommended if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5-2.0 g/l.¹⁹⁰ However, a recent Cochrane review by Wikkelsø et al. investigated the evidence for the use of fibrinogen concentrate in bleeding patients and stated that evidence is sparse and randomized controlled studies are lacking.¹⁶ It is also important to address if there is an associated delayed risk of thrombosis after use of fibrinogen concentrate. In rAAA the use of fibrinogen concentrate should be further evaluated.²¹³ Prospective randomized trials, as suggested above, could answer some of these questions.

The overall perfect hemostasis measurement method is still not available. Most centers use standard coagulation tests in clinical practice, even though these tests were not developed to guide coagulation management in the emergency surgical situation.²²⁴ In *Paper III* the

commonly used laboratory markers were investigated in relation to blood pressure and outcome in rAAA. Viscoelastic testing is on the rise and studies are performed especially in the field of trauma. Exciting and promising data have originated from clinical evaluations of the tests in various fields of medical practice.²²⁸ However, the methods have limitations. In all known coagulation testing, blood is removed from the patient and the total functionality cannot yet be tested on site in the blood vessels. A future goal is to transfer the methods of evaluation and treatment into the site of action, and by expeditious methods instantly be able to diagnose, correct and treat an impaired hemostatic process. Spray pulses of concentrated coagulation factors where best needed in the body through injections by needles, LRTs and/or catheters might be possible treatment options to explore.

Patients undergoing AAA repair are often subject to blood transfusion. It is by now well described that the ratios between blood products influence outcome in other surgical fields. The comorbidities and severity of the AAA disease offer special considerations when transfusing these patients massively. A goal driven transfusion strategy would probably best suit this patient cohort and a practice of arbitrary transfusion of blood products should be avoided. The rapid start of transfusing platelets in massively bleeding patients seems to affect the outcome (*Paper IV*) in rAAA patients. This raises questions of early detection of the potential need to do so and if this can be accomplished by better routines and increased awareness. Quick off the shelf supply is only available to a limited extent. In order to further explore this key topic, prospective data collection and future randomized controlled trials are required.

Vascular surgeons are regularly engaged as specialists in controlling surgical bleedings in different parts of the body and not only in relation to vascular diseases and vascular surgery complications and iatrogenic vascular injuries. Vascular surgeons are also often used as advisors in thromboembolic events in arteries as well as in veins. The management of bleeding, coagulopathy and thrombosis is a moving target where the development over the last years challenges old truths and physicians to keep updated. In order to meet the expectations from patients and colleagues the vascular surgeon must be equipped with the adequate knowledge and a powerful armament to fight bleeding. Above all the vascular surgeon needs to embrace the motto of Sir Robert Baden Powell and the Scout movement:

-Be prepared!

-Always prepared!

6 CONCLUSIONS

- The fascia suture technique was shown to be a safe, effective, and simple method to gain hemostasis at the femoral access sites after EVAR. It was effective also after large diameter introducers up to 24 Fr. No specific preoperative risk factor for the failure of fascia suture technique was found. It was deemed as a valid alternative to other techniques of obtaining postoperative hemostasis and has economic advantages.
- Large perioperative hemorrhage during EVAR was found to be a clinical problem that affects outcome. Efforts must be made to minimize perioperative blood loss.
- A perioperative blood loss exceeding 2 liters was independently associated with increased mortality and morbidity in both acute and elective AAA patients. Open femoral access, branched EVAR and larger diameter introducers were associated with increased perioperative blood loss.
- Low preoperative fibrinogen concentration was significantly associated with preoperative hypotension and increased perioperative bleeding. Hypofibrinogenemia should be suspected in preoperative hypotension (<70mmHg).
- Preoperative fibrinogen concentrations below 1.5 g/L were associated with a ten-fold increased risk of perioperative bleeding of more than 2 liters. Future studies need to investigate the potential benefit of early treatment with fibrinogen concentrate in patients with rAAA and hemodynamic shock.
- In massively transfused rAAA patients, EVAR was associated with smaller transfusion volumes and with lower FFP:RBC and PLT:RBC ratios compared to open repair. More than half of rAAA patients repaired by EVAR required massive transfusion.
- Lower risk of mortality was seen in patients with FFP:RBC ratios of close to 1:1 in EVAR and open repaired AAA patients.
- Delayed (>1h) platelet transfusion in patients with rAAA requiring massive transfusion was associated with significantly increased mortality.
- Ratios of PLT:RBC have increased over the last years. Transfusion strategies, in patients undergoing rAAA treatment with EVAR or open repair, need further research.

7 SAMMANFATTNING PÅ SVENSKA

Avhandlingens bakgrund och syfte:

Det övergripande syftet med avhandlingen var att studera olika aspekter av blödningsproblematik vid behandling av bukaortaaneurysm (BAA), på engelska *abdominal aortic aneurysm* (AAA).

Blödning vid operation av AAA kan vara betydande. Vid minimalinvasiv endovaskulär behandling (endovascular aortic aneurysm repair, EVAR) behandlas den sjuka kroppspulsådern med ett så kallad stentgraft som placeras på insidan av kroppspulsådern, ofta med mindre blödningsproblematik jämfört med öppen kirurgi. Det är känt att blödning i samband med operation påverkar resultatet, men få studier har undersökt problemen relaterade till blödning vid behandling av AAA. För EVAR finns relativt få studier som analyserar just blödningsproblematik.

Blödning under ingreppet, prediktiva markörer och blodtransfusion vid öppen kirurgi och EVAR studerades i fyra olika studier. Både planerade och akuta behandlingar av AAA undersöktes.

Det specifika syftet med studierna var:

- Att undersöka användbarhet, säkerhet, resultat och eventuella faktorer som påverkar utfallet vid användning av en särskild operationsteknik för blödningskontroll i ljumskpulsådern efter EVAR. Operationstekniken kallas *Fascia Suture Technique* och förkortas FST.
- Att studera blödningsvolym och dess relation till resultat vid EVAR vad gäller både akuta och planerade ingrepp.
- Att studera laboratorieprover avseende blodets förmåga att levera sig, tagna före operation, hos patienter med brustet AAA samt att relatera dessa till resultat och patientens blodtryck före behandling.
- Att studera förhållandet mellan givna blodtransfusioner och resultat vid brustna AAA hos patienter som genomgår EVAR eller öppen kirurgi. Vi studerade tidsaspekter och förhållanden mellan antal enheter av röda blodkroppar, plasma och blodplättar (trombocyter) som givits.

Patienter och metoder:

Samtliga studier var retrospektiva och baserades på patientjournaler samt regionala och nationella register (*Studie II-IV*). I *Studie I* undersöktes 160 FST som operativ förslutningsmetod för blödningskontroll av ljumskkärlsinfart efter EVAR. Vi granskade datortomografibilder tagna före och ett år efter operation. *Studie II* analyserade brustna och icke-brustna AAA bland 525 patienter som genomgick antingen öppen eller endovaskulär behandling. Korrelationen mellan blödning under operationen och mortalitet och morbiditet undersöktes. I *Studie III* undersöktes 91 patienter med brustna AAA avseende

laboratorieanalyser av blodets förmåga att levera sig och deras förhållande till lågt blodtryck före operation, blödningsvolym och komplikationer. I *Studie IV* undersöktes blodtransfusion av 369 patienter med brustet AAA som genomgått öppen eller endovaskulär behandling. Tidpunkt för blodtransfusion och tidsberoende förhållanden av givna blodprodukter studerades och relaterades till metod för kirurgisk behandling och resultat. Olika statistiska metoder användes för att utvärdera eventuella samband.

Resultat:

Studie I visade att 91 % av FST utfördes med lyckat resultat. Få komplikationer uppstod och inga tydliga riskfaktorer för negativt utfall av metoden hittades. I *Studie II* fann man att en blödning av >2 liter under ingreppet var oberoende relaterat till ökad dödlighet och komplikationer (njurskada, multiorgansvikt, >5 dagar på intensivvårdsavdelning, bristande blodflöde till tarmen samt ökat buktryck) bland planerade och brustna AAA. I *Studie III* visades att lågt fibrinogen värde (<1.5 g/L) i plasma var associerat med lågt blodtryck (systoliskt blodtryck <70 mmHg), ökad blödning och sämre resultat. *Studie IV* visade att fördröjd trombocytttransfusion (>1h) var associerad med ökad dödlighet hos patienter med brustna AAA som krävde massiv transfusion (>10 enheter röda blodkroppar (RBC) inom 24 timmar eller 4 enheter RBC inom en timme). Transfusionsförhållandet av kvoten 1:1 mellan given färskfrusen plasma (FFP) i förhållande till RBC var associerat med lägre dödlighet. Förhållandet mellan givna trombocytkoncentrat (PLT) och RBC ökade under studieperioden.

Slutsatser:

- *Fascia Suture Technique* visade sig vara en enkel och säker teknik med ett lågt antal komplikationer. Inga preoperativa riskfaktorer identifierades.
- En blodförlust större än två liter vid operation med EVAR visades ha ett oberoende samband med ökad dödlighet och sjuklighet vid både akuta och planerade AAA ingrepp. Öppen operation för åtkomst av ljumskärl, grenade EVAR och större diameter av införingsinstrument var relaterat till ökad blodförlust.
- Hos patienter med fibrinogenkoncentrationer mindre än 1,5 g/L före operation förelåg en tio-faldigt ökad risk för intraoperativ blödning på mer än 2 liter vid brustna AAA. Lågt fibrinogen skall misstänkas vid lågt blodtryck (<70mmHg) vid brustna AAA.
- Massiv transfusion erfordrades bland 55 % av patienter med brustna AAA behandlade med EVAR. Ett kvotförhållande mellan FFP och RBC nära 1:1 vid såväl EVAR som öppet opererade patienter var förenat med lägre dödlighet.
- Fördröjd (>1h) transfusion av trombocytkoncentrat var förenat med signifikant ökad dödlighet. Transfusionskvotförhållandet mellan PLT och RBC ökade under studietiden.
- Transfusionsstrategier hos patienter som genomgår behandling med EVAR eller öppen behandling efter brustet AAA, kräver ytterligare forskning. Användning av fibrinogenkoncentrat hos patienter med brustet AAA och lågt blodtryck behöver ytterligare utredas.

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